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*NMS Obstetrics
and Gynecology*

NMS *Obstetrics and Gynecology*

7th EDITION

Editor

Samantha M. Pfeifer, MD

Associate Professor

Obstetrics and Gynecology

Division of Reproductive Endocrinology and Infertility

University of Pennsylvania Medical School

Philadelphia, Pennsylvania



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This book is dedicated to the memory of my mentors Dr. Luigi Mastroianni and Dr. Celso-Ramon Garcia, who set an example of excellence in teaching and clinical care of patients. I would also like to dedicate this to Alice and Charlotte Rose for their support and encouragement.



Contributors

Joanna Adamczak, MD

Instructor, Obstetrics and Gynecology
Division of Maternal Fetal Medicine
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Dacarla M. Albright, MD

Clinical Associate, Obstetrics and Gynecology
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Lily Arya, MD, MS

Associate Professor, Obstetrics & Gynecology
Chief, Division of Gynecologic Urology and
Pelvic Reconstructive Surgery
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Janice B. Asher, MD

Clinical Associate Professor Obstetrics and
Gynecology
Clinical Director, Women's Health
Student Health Services
University of Pennsylvania
Philadelphia, Pennsylvania

Thomas J. Bader, MD

Associate Professor, Obstetrics and Gynecology
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Kurt Barnhart, MD, MSCE

Professor of Obstetrics & Gynecology and
Epidemiology
Director, Women's Health Clinical Research
Center
Assistant Dean Clinical research Operations
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Mathew N. Beshara, MD

Assistant Professor of Clinical Obstetrics and
Gynecology
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Marcia Boraas, MD

Clinical Associate Professor, Department of
Surgery
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Danielle Burkland, MD

Assistant Professor of Clinical Obstetrics and
Gynecology
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Samantha F. Butts, MD, MSCE

Assistant Professor, Obstetrics and Gynecology
Division of Reproductive Endocrinology and
Infertility
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Diana Chavkin, MD

Instructor, Obstetrics and Gynecology
Division of Reproductive Endocrinology and
Infertility
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Peter J. Chen, MD

Assistant Professor, Obstetrics and Gynecology
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Christina S. Chu, MD

Assistant Professor, Obstetrics and Gynecology
Division of Gynecologic Oncology
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Janell S. Coleman, MD

Assistant Clinical Professor, Obstetrics and
Gynecology
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Anuja Dokras, MD, PhD

Associate Professor, Obstetrics and Gynecology
 Medical Director, In Vitro Fertilization
 Perelman School of Medicine at the University
 of Pennsylvania
 Philadelphia, Pennsylvania

Scott E. Edwards, MD

Assistant Professor of Clinical Obstetrics and
 Gynecology
 Division of Reproductive Endocrinology and
 Infertility
 Perelman School of Medicine at the University
 of Pennsylvania
 Philadelphia, Pennsylvania

Michal A. Elovitz, MD

Associate Professor of Obstetrics and Gynecology
 Division of Maternal Fetal Medicine
 Perelman School of Medicine at the University
 of Pennsylvania
 Philadelphia, Pennsylvania

Alex Friedmas, MD, MS, MPH

Instructor, Obstetrics and Gynecology
 Perelman School of Medicine at the University
 of Pennsylvania
 Philadelphia, Pennsylvania

Robert Gaiser, MD

Professor, Department of Anesthesiology and
 Critical Care
 Perelman School of Medicine at the University
 of Pennsylvania
 Philadelphia, Pennsylvania

Clarisa Gracia, MD, MSCE

Assistant Professor, Obstetrics and Gynecology
 Division of Reproductive Endocrinology and
 Infertility
 Perelman School of Medicine at the University
 of Pennsylvania
 Philadelphia, Pennsylvania

Andrea R. Hagemann, MD

Instructor, Obstetrics and Gynecology and
 Infertility
 Division of Gynecologic Oncology
 Perelman School of Medicine at the University
 of Pennsylvania
 Philadelphia, Pennsylvania

Ann Honebrink, MD

Associate Professor of Clinical Obstetrics and
 Gynecology
 Medical Director, Penn Health for Women at
 Radnor
 Perelman School of Medicine at the University
 of Pennsylvania
 Philadelphia, Pennsylvania

Vanita Dharan Jain, MD

Instructor, Obstetrics and Gynecology
 Division of Maternal Fetal Medicine
 Perelman School of Medicine at the University
 of Pennsylvania
 Philadelphia, Pennsylvania

Abike T. James, MD, MPH

Assistant Professor of Clinical Obstetrics and
 Gynecology
 Perelman School of Medicine at the University
 of Pennsylvania
 Philadelphia, Pennsylvania

Suleena Kansal Kalra, MD, MSCE

Assistant Professor, Obstetrics and Gynecology
 Division of Reproductive Endocrinology and
 Infertility
 Perelman School of Medicine at the University
 of Pennsylvania
 Philadelphia, Pennsylvania

Maureen Kelly, MD

Clinical Associate Professor, Obstetrics and
 Gynecology
 Division of Reproductive Endocrinology and
 Infertility
 Perelman School of Medicine at the University
 of Pennsylvania
 Philadelphia, Pennsylvania

Laxmi A. Kondapalli, MD

Instructor, Obstetrics and Gynecology
 Division of Reproductive Endocrinology and
 Infertility
 Perelman School of Medicine at the University
 of Pennsylvania
 Philadelphia, Pennsylvania

Jack Ludmir, MD

Professor and Chair, Department of
 Obstetrics & Gynecology at Pennsylvania
 Hospital and
 Vice Chair, Department of Obstetrics &
 Gynecology, Director OB Services
 Hospital of the University of Pennsylvania
 Philadelphia, Pennsylvania

Monica A. Mainigi, MD

Instructor, Obstetrics and Gynecology
 Division of Reproductive Endocrinology and
 Infertility
 Perelman School of Medicine at the University
 of Pennsylvania
 Philadelphia, Pennsylvania

Winifred Mak, MD, PhD

Instructor, Obstetrics and Gynecology
Division of Reproductive Endocrinology and
Infertility
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Dominic Marchiano, MD

Assistant Professor of Clinical Obstetrics and
Gynecology
Division of Maternal Fetal Medicine
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Evelyn B. Marsh, MD

Instructor, Obstetrics and gynecology
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Janet F. McLaren, MD, MSCE

Instructor, Obstetrics and Gynecology
Division of Reproductive Endocrinology and
Infertility
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Lauren W. Milman, MD

Instructor, Obstetrics and Gynecology
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Emmanuelle Pare, MD

Assistant Professor, Obstetrics and Gynecology
Division of Maternal Fetal Medicine
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Samantha M. Pfeifer, MD

Associate Professor Obstetrics & Gynecology
Division of Reproductive Endocrinology and
Infertility
Director of Reproductive Surgery
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Sara Pittenger, MD

Instructor, Obstetrics and Gynecology
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Mary E. Rausch, MD, MSCE

Instructor, Obstetrics and Gynecology
Division of Reproductive Endocrinology and
Infertility
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Catherine R. Salva, MD

Assistant Professor of Clinical Obstetrics and
Gynecology
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Isaac E. Sasson, MD, PhD

Instructor, Obstetrics and Gynecology
Division of Reproductive Endocrinology and
Infertility
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Courtney A. Schreiber, MD, MPH

Assistant Professor, Obstetrics and Gynecology
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Nadav Schwartz, MD

Assistant Professor, Obstetrics and Gynecology
Division of Maternal Fetal Medicine
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Saya Segal, MD

Instructor, Obstetrics and Gynecology
Division of Gynecologic Urology and Pelvic
Reconstructive Surgery
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Harish M. Sehdev, MD

Assistant Professor Clinical Obstetrics &
Gynecology
Director, Perinatal Diagnosis at Pennsylvania
Hospital
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Steven J. Sondheimer, MD

Professor, Obstetrics and Gynecology
Division of Reproductive Endocrinology and
Infertility
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Peter J. Vasquez, MD

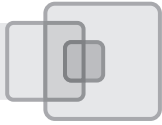
Instructor, Obstetrics and Gynecology
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Eileen Wang, MD

Assistant Professor, Obstetrics and Gynecology
Division of Maternal Fetal Medicine
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Yu-Hsin Wu, MD

Assistant Professor of Clinical Obstetrics and
Gynecology
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

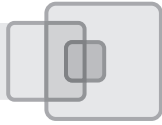


Preface

The seventh edition of *NMS Obstetrics and Gynecology* has the same primary goal of the previous edition, and, indeed, the entire NMS series—to provide the most up-to-date and relevant information in an easy-to-understand outline format for both students and residents. Basic scientific information is balanced by clinical relevance, and a wealth of more than 200 USMLE-formatted questions allows readers to test their knowledge prior to their board examinations.

This seventh edition represents a collaborative effort between the many contributors who revised existing chapters or wrote new chapters for this edition, and the new editor, Samantha M. Pfeifer, who orchestrated and oversaw the text revision, as well as revamped the USMLE-style questions and online Comprehensive Examination to reflect current Step 2 formats and content areas. The 60 questions in the Comprehensive Examination, available online on The Point (thepoint.lww.com), have been written at a slightly higher level of difficulty than the USMLE-formatted questions in the chapters. Some of the answers, therefore, require a level of knowledge that goes beyond the information presented in the book. The examination thus provides a rigorous and comprehensive review of content.

The content covered in all of the chapters has been thoroughly updated. One new chapter has been added, Chapter 21, Müllerian Anomalies and Disorders of Sexual Development. In addition, five chapters have been significantly revised, including Chapter 18, The Gynecologic Office Visit; Chapter 25, Hirsutism and Other Hyperandrogenic Disorders; Chapter 26, Pelvic Pain; Chapter 28, Uterine Leiomyomas; and Chapter 38, Breast Disease. In addition, the order of the chapters has been rearranged to make the order of presentation more logical, although the chapters can be used in any order. The online case studies, also available on The Point, have been rewritten to reflect current treatment paradigms and incorporate new information that is available and influences the diagnosis and treatment of the specific conditions.



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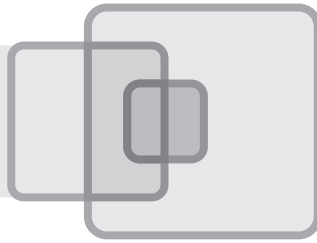
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Endocrinology of Pregnancy

JOANNA ADAMCZAK • EILEEN WANG

I

INTRODUCTION

Endocrine changes in pregnancy are largely dependent on the concerted production of protein and steroid hormones by the fetoplacental unit. The mother undergoes profound changes from conception onward through parturition, then reverting to the nonpregnant state a few weeks after delivery. Initially, the mother is the exclusive source of certain hormones (such as estrogen and progesterone) early in pregnancy; however, by the end of the first trimester the fetus and placenta become important sources of steroid and protein hormones production. During the course of pregnancy virtually all maternal endocrine glands are affected by gestation; these endocrine changes support the successful establishment, maintenance, and completion of pregnancy.

A Endocrine changes during pregnancy The fetal–placental–maternal unit can be viewed as a well-orchestrated unit that functions together in an integrated fashion to control the physiologic needs of gestation. The function of each is paramount in the success of a pregnancy. One of the most important endocrine changes involves the production of protein hormones (human chorionic gonadotropin [hCG] and human chorionic somatomammotropin [hCS], once called human placental lactogen [hPL]) and **steroid hormones** (estrogen and progesterone). The contribution of each—placenta, fetus, and mother—will be reviewed here.

1. **Placenta.** The placenta has a diverse secretory repertoire that surpasses that of any other endocrine organ. What is remarkable is that the placenta is not innervated and has no neuronal connections to either the fetal or the maternal glands. While the placental products are responsible for the release of hormones into both the fetal and the maternal circulation, the cytotrophoblast–syncytiotrophoblast relationship can also be comparable to the hypothalamic–pituitary relationship given the paracrine and autocrine actions of placental signaling molecules.
 - a. Endocrine organ consists of essentially two cell types—syncytiotrophoblasts and cytotrophoblasts.
 - b. It secretes large quantities of estrogen and progesterone, **gonadotropin-releasing hormone (GnRH)**, **corticotropin-releasing hormone (CRH)**, and **thyrotropin-releasing hormone (TRH)**.
2. **Fetus.** The fetal endocrine glands (e.g., pituitary, thyroid, adrenal cortex, pancreas, and gonads) function as early as the 11th week of gestation.
 - a. In the male fetus, the Leydig cells of the testes, in response to placental gonadotropin and initially to hCG, produce testosterone, which is necessary for normal male external and internal genitalia development.
 - b. The maternal environment is not greatly impacted by fetal testosterone due to the placental enzyme aromatase, which converts testosterone to estradiol.
 - c. In the female fetus, the ovary is not active and does not secrete estrogens until puberty, although all future oocytes are already present.
 - d. Placenta cannot convert pregnenolone to androgens. Progesterone enters the fetal circulation where the fetal adrenal gland can convert it to androgens, making the fetal adrenal cortex the primary provider of the immediate androgen precursors of placental estrogen (Fig. 1–1).

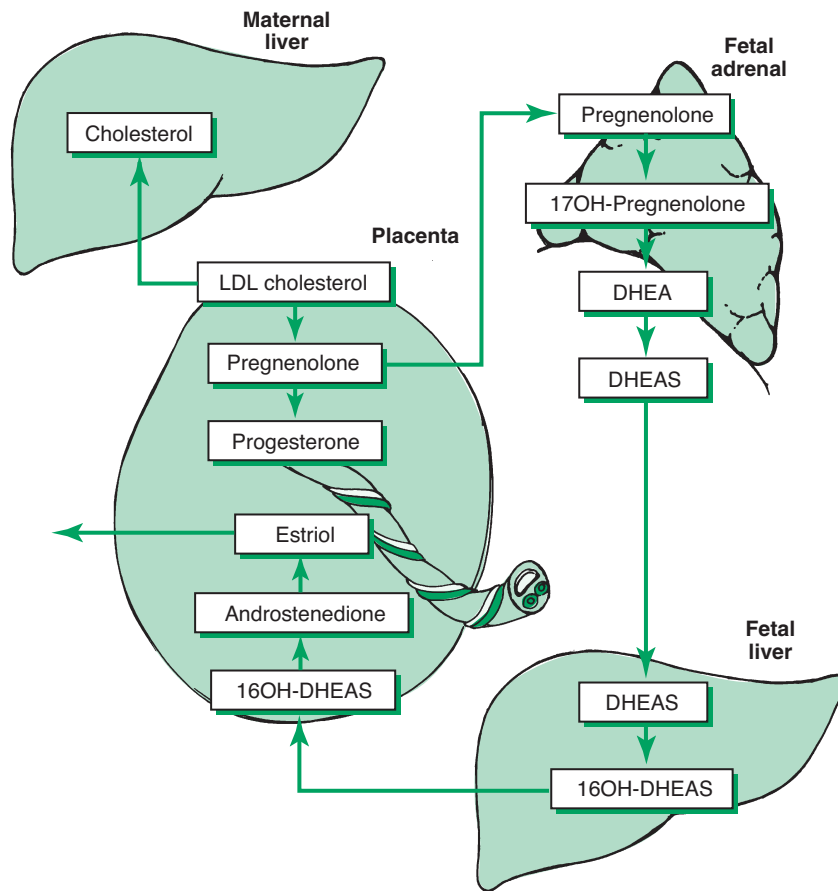


FIGURE 1–1 Schematic representation of estrogen and progesterone synthesis in late pregnancy. DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfate; LDL, low-density lipoprotein.

3. Maternal endocrine changes. Essentially every maternal endocrine gland (e.g., hypothalamus, pituitary, thyroid, and adrenal) supports the appropriate interactions of the fetal–placental–maternal unit.

a. Hypothalamus. As in the nonpregnant state, the hypothalamic–pituitary axis through cell-to-cell communication regulates much of the necessary endocrine functions.

- (1) Corticotropin-releasing hormone is elevated during pregnancy in maternal circulation and rises exponentially throughout gestation.
- (2) This stimulates an increase in adrenocorticotrophic hormone (ACTH) which then leads to greater amounts of serum, salivary, and urinary-free cortisol, making pregnancy a state of relative hypercortisolism.

b. Pituitary. Pregnancy is associated with a variety of changes in hormones released from the pituitary gland.

- (1) Decline in gonadotropin, likely due to the high estradiol and progesterone concentrations acting centrally.
- (2) Decline in pituitary-derived growth hormone, which is replaced by placental-derived growth hormone.
- (3) Thyrotropin (TSH) secretion falls subtly during early pregnancy with an increase in free thyroxine because of the structurally related thyroid-stimulating activity of hCG.
- (4) Oxytocin concentrations from the posterior lobe of the pituitary rise continuously across gestation.

c. Thyroid. There are well-described changes in thyroid function tests during pregnancy.

- (1) There is estrogen-mediated increase in circulating levels of thyroid-binding globulin (TBG) which is the major transport protein for thyroid hormone.

- (2) This leads to an increase in both serum total thyroxine (T4) and triiodothyronine (T3), but not the physiologically important free T4 and T3 concentrations, thus the metabolic processes that are dependent on these hormones are usually unaltered.
- d. Adrenal gland.** The renin–angiotensin–aldosterone system is stimulated during pregnancy, with a substantial increase in aldosterone levels seen by the eighth week of gestation.

B Hormones during pregnancy Understanding the function of a particular hormone may illuminate its role in reproductive physiology, particularly in maintaining pregnancy and fetal well-being. The hormones discussed below are synthesized by the placenta, mother, and fetus. Occasionally, hormones have multiple sources. For example, the mother, the placenta, and the fetus all produce estradiol. The hormones essential for a successful pregnancy can be split into two categories: **protein hormones** (e.g., hCG, hCS, and prolactin) and **steroids** (e.g., progesterone, estrogen, and fetal adrenal steroids).

C Human chorionic gonadotropin

1. Definition

- a. hCG is a glycoprotein composed of two subunits, α and β , that are noncovalently linked.
- b. The α -subunit of hCG is biochemically homologous to thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH).
- c. The β -subunit of hCG is similar to LH, differing by only 30 amino acids.
- d. After implantation, hCG is almost exclusively the product of the trophoblastic tissue, specifically the syncytiotrophoblast. It is one of the earliest products of the cells forming the embryo; hCG is produced by normal placental tissue as early as 6 to 8 days postconception.
- e. The level of hCG then rises rapidly, doubling every 2 to 3 days until approximately 6 weeks' gestation, at which point the rate of rise decreases. This exponential rise allows clinicians to differentiate normal from abnormal gestations, i.e., miscarriage or ectopic pregnancy.
- f. The hCG level reaches a peak at approximately 8 to 9 weeks' gestation, after which the level declines to a plateau and remains detectable throughout the remainder of the pregnancy.

2. Clinical use: marker of pregnancy

- a. hCG is the earliest biochemical marker for pregnancy and can be detected in either serum 3 to 4 days before expected menses. Serum assays can detect hCG earlier than urine assays and can provide specific quantification of levels, unlike the urine assay which only identifies presence of the hormone.
- b. After delivery at term, hCG can normally be detected in the mother for up to 4 weeks.
- c. After the first-trimester miscarriage or elective termination of pregnancy, hCG can be detected in the maternal serum or urine for as long as 10 weeks.
- d. Quantitative serum hCG values can be used to assess the viability of a pregnancy by correlating them with ultrasound findings of pregnancy. When the serum hCG value exceeds 2,000 mIU/mL, a gestational sac should be visible on transvaginal ultrasound, with higher thresholds needed to visualize the yolk sac and embryo.

3. Clinical use: screening for chromosome abnormalities

- a. Additionally, hCG is used as a component for maternal serum screening for chromosomal abnormalities (see chapter on Prenatal Diagnosis).
- b. In the first-trimester free β -hCG and pregnancy-associated plasma protein A (PAPP-A) combined with an ultrasound measurement, nuchal translucency (NT), allows for screening for Down syndrome and trisomy 18.
- c. In the second trimester, if the first-trimester screening has not been done, maternal serum hCG, α -fetoprotein, inhibin-A (a dimer produced by the placenta), and unconjugated estriol represent the quadruple screen used to screen for Down syndrome, trisomy 18, and open neural tube defects. During the second trimester, elevated hCG is the most sensitive serum marker for Down syndrome.
- d. hCG can be used to monitor disease progression/remission in patients with trophoblastic neoplasia who present with very elevated hCG levels.

4. Biologic functions

- a. The chief biologic function of hCG during early gestation is to signal the ovary to maintain the corpus luteum and continue progesterone production. This happens until about the tenth week of gestation after which time the placenta takes over progesterone synthesis.
- b. **Significance of abnormally high levels of hCG**
 - (1) Multiple placentas (multiple gestation)
 - (2) Hydatidiform mole by virtue of trophoblastic proliferation
 - (3) Choriocarcinoma
- c. **Significance of abnormally low levels of hCG**
 - (1) Ectopic pregnancy
 - (2) Miscarriage

D Human chorionic somatomammotropin, a/k/a human placental lactogen**1. Definition**

- a. hCS is a single-chain peptide hormone, with structural, immunologic, and biologic similarities to both pituitary growth hormone and prolactin.
- b. It is formed by the placenta as early as 3 weeks' postconception and is secreted by the syncytiotrophoblast.
- c. hCS can be detected in maternal serum as early as 6 weeks' postconception. Like most hormones produced by the syncytiotrophoblast, hCS is secreted primarily into the maternal bloodstream.
- d. The levels rise in maternal serum until 34 weeks' gestation and then plateau, with levels correlating to an increasing placental mass. At term it is the most abundant secretory product of the placenta.

2. Biologic function

- a. The principal action of hCS is to increase the supply of glucose to the fetus, it does this by altering maternal secretion of insulin. hCS induces lipolysis and increases maternal-free fatty acids, ketones, and glycerol, which provide energy for the mother.
- b. In the maternal fasting state, glucose crosses the placenta and serves as fuel for the fetus leaving free fatty acids for maternal use. In the fed state, free fatty acids interfere with insulin-directed entry of glucose into cells allowing for glucose passage across the placenta.
- c. It has been postulated that hCS acts as the "growth hormone" of pregnancy to ensure the nutritional demands of the fetus.

3. Clinical use

- a. Although early studies have shown that the low-maternal serum levels of hCS are associated with fetal growth restriction and nonreassuring fetal heart rate patterns, subsequent studies have been unable to substantiate the value of hCS monitoring for detecting fetal complications secondary to uteroplacental insufficiency.
- b. Normal pregnancies resulting in the delivery of health infants have been reported in individuals with very low synthesis of hCS. It is possible that hCS is not essential for pregnancy and may serve as an evolutionary redundancy.

E Prolactin**1. Definition**

- a. Prolactin is a protein hormone that circulates in different molecular sizes. The three potential sources of prolactin during pregnancy are as follows:
 - (1) Anterior lobe of the maternal pituitary gland, which is the primary source of elevated maternal serum prolactin levels.
 - (2) Anterior lobe of the fetal pituitary gland.
 - (3) Decidual tissue of the uterus, from which prolactin is secreted primarily into the amniotic fluid but can elevate the maternal serum level.
- b. In the nonpregnant state, prolactin levels normally range between 8 and 25 ng/mL.
- c. During pregnancy, maternal prolactin levels increase under the influence of estrogen to a maximum of 200 ng/mL in the third trimester. Levels of prolactin in pregnancy should not be interpreted as indicative of pituitary adenoma growth. However, women with prolactin-secreting adenomas who conceive should be monitored by visual field determinations for the possibility of enlargement.

2. Biologic function

- a. The principal function of prolactin is preparing the mammary glands for lactation. It stimulates the growth of mammary tissue and production and secretion of milk into the alveoli.
- b. During pregnancy, lactation does not occur because estrogen inhibits the action of prolactin on the breast.
- c. Decidual prolactin is thought to be important for fluid and electrolyte regulation of the amniotic fluid.

F Progesterone

1. Definition

- a. Progesterone is a 21-carbon steroid hormone derived from cholesterol.
- b. In nonpregnant women, progesterone is produced primarily by the ovaries and adrenal cortex. It serves as an intermediary for other hormones (e.g., aldosterone, cortisol, estrogen, and testosterone) and as an end-product when it is produced by the corpus luteum.
- c. In the pregnant state, progesterone initially has a dual source. It is produced by the corpus luteum until the tenth week of pregnancy and is essential for pregnancy maintenance until 8 to 9 weeks.
- d. The placenta then takes over as the primary source of progesterone production at about 8 weeks' gestation and continues until parturition and the corpus luteum becomes an insignificant source of progesterone.
- e. Progesterone concentrations in the blood continue to increase up until the time of onset of labor, at which time the placenta produces 300 mg/d; most of the progesterone produced enters the maternal circulation.
- f. Progesterone is produced in larger quantities in the presence of multiple gestations.

2. Biologic functions

- a. The primary function of progesterone is to support the pregnancy, it does this through mediation of many important biological roles throughout gestation.
- b. Initially, it prepares the endometrium for implantation of the embryo.
- c. Progesterone suppresses the calcium–calmodulin–myosin light chain kinase system in smooth muscle, thereby suppressing uterine contractions, as well as acting on smooth muscle in other organs including blood vessels, ureters, and intestines. These effects of progesterone appear to be receptor-mediated and can be blocked by the progesterone receptor antagonist mifepristone (RU486), which is used as an abortifacient in the first trimester.
- d. Progesterone also prevents rejection of the fetus by the maternal immune system, through anti-inflammatory and immunosuppressive functions. Specifically, progesterone suppresses T-lymphocyte production of cytolytic cytokines. Additionally, its function is integral in creating a barrier to penetration of pathogens into the uterus.

G Estrogens

1. Definition

- a. Estrogens are 18-carbon steroid hormones that possess an aromatic ring. Three types of estrogens exist during pregnancy and differ by the number of hydroxyl groups they contain.
 - (1) **Estrone**, a relatively weak estrogen, has one hydroxyl group.
 - (2) **Estradiol**, the most potent estrogen, produced primarily by the granulosa cells in developing follicles, contains two hydroxyl groups.
 - (3) **Estriol**, a very weak estrogen, contains three hydroxyl groups. Estriol is produced in extremely large quantities by the placenta during pregnancy and is the major estrogen formed during pregnancy.
- b. Early pregnancy: estradiol is the major form of estrogen present and is produced by maternal ovaries.
- c. Later in pregnancy, estrone and estradiol are produced primarily by the placenta, and estriol is produced almost exclusively by the placenta.
- d. Significant amounts of estriol are produced early in the second trimester, and levels continue to rise until parturition, increasing 1,000-fold over the nonpregnant level.

- e. **Synthesis of estrogen** involves coordination of metabolic steps in the mother, the placenta, and the fetus (see Fig. 1–1).
 - (1) Estrogens cannot be produced *de novo* in the placenta because the placenta lacks the enzyme activity necessary to convert pregnenolone to androgen precursors (17 α -hydroxylase and 17 to 20 lyase).
 - (2) The fetal adrenal cortex converts pregnenolone to dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS), which is then converted to 16-OH DHEAS in the fetal liver.
 - (3) 16-OH DHEAS is then converted to androgen precursors and aromatized to estrogen in the placenta.
 - f. Affinity to sex hormone-binding globulin (SHBG) differs among the three estrogens: estradiol is largely bound to SHBG in the maternal serum, whereas estriol remains unbound. Since unbound estriol is preferentially excreted in the urine, maternal serum levels of estradiol are higher than those of estriol.
2. **Biologic activities.** Because placental estrogen formation is dependent on androgenic precursors produced by the fetal adrenal cortex, the fetus is required for many of the maternal physiologic effects mediated by estrogen.
- a. Estrogen increases blood flow to the uterus, which ensures an adequate supply of oxygen and nutrients to the fetus.
 - b. Estrogen allows for an increase in the maternal hepatic production of binding proteins such as TBG and cortisol-binding globulin (CBG).
 - c. Estrogen plays a role in inhibiting maternal pituitary gonadotropin synthesis and release; placental gonadotropins are primarily responsible for gonadotropic function.
 - d. Estrogen-enhanced placental production of 11 α -hydroxysteroid dehydrogenase (11 α -HSD) inactivates maternal cortisol, thereby isolating the fetal pituitary and adrenal from maternal influences.
 - e. Estrogen stimulates receptor-mediated low-density lipoprotein (LDL) uptake by the placenta and placental expression of enzymes which are important in steroidogenesis.
 - f. Estrogen activates oxytocin secretion and myometrial gap junction formation during parturition. Measurement of maternal salivary estriol levels has been proposed as a predictor of preterm birth. Labor and delivery may be delayed in anencephalic fetuses and fetuses with placental sulfatase deficiency when large amounts of estrogen cannot be produced.
 - g. Estrogen stimulates epithelial cell proliferation in human breast tissue during lactation. However, milk release is delayed until estrogen levels decrease after delivery.
3. **Clinical significance.** Because estriol is an index of normal function of the fetus and the placenta, reduced maternal estriol levels may reflect abnormalities in fetal or placental development. Extremely low levels or no estriol may be associated with:
- a. Fetal demise.
 - b. Anencephaly: the limited ACTH production results in atrophy of the fetal zone of the adrenal cortex after 20 weeks' gestation.
 - c. Placental sulfatase deficiency.



Study Questions for Chapter 1

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A 26-year-old female presents to the emergency room complaining of severe right lower quadrant pain. She is immediately taken to the operating room for presumed appendicitis. At the time of her surgery her appendix is normal. The surgeon sees a large mass on the right ovary and removes the ovary. Frozen section on the mass shows a corpus luteum. Immediately after the surgery her pregnancy test is found to be positive. She is, by dates 6 weeks' pregnant. You are called as the consulting gynecologist. Your main concern is the following:

- ☐ A The hCG level should double over the next 2 days since she is 6 weeks' pregnant
- ☐ B Having one ovary will affect her ability to produce hormones
- ☐ C Removing the corpus luteum will affect the pregnancy
- ☐ D Estrogen production will not be affected

2. A 36-year-old woman, gravida 3, para 2, at 8 weeks' gestation, presents to your clinic reporting painless vaginal bleeding. Her vital signs are as follows: T = 99.9, BP = 162/94, P = 100, and R = 18. Her uterus is consistent with a 14-week pregnancy. Her serum hCG level is 320,000 IU/L. Which of the following endocrine glands is most likely to be affected by hCG?

- ☐ A Adrenal cortex
- ☐ B Hypothalamus
- ☐ C Ovary
- ☐ D Parathyroid
- ☐ E Thyroid

3. A 29-year-old woman who is pregnant calls you for advice. She has just found out that her hCG level is elevated. Which of the following is true?

- ☐ A hCG can stimulate production of TRH, causing hyperthyroidism
- ☐ B A high level of hCG is indicative of an ectopic pregnancy
- ☐ C A high level of hCG in the second trimester is indicative of an impending miscarriage pregnancy
- ☐ D A high level of hCG in the second trimester is the most sensitive marker for Down syndrome
- ☐ E hCG is part of the quadruple screen in the first trimester

4. Estrogens are produced by the mother, fetus, and placenta. Which one of the following is true?

- ☐ A Estradiol accounts for 80% of the estrogen produced during pregnancy
- ☐ B Estriol is produced primarily by the placenta
- ☐ C Anencephaly is associated with a normal level of estriol
- ☐ D Estrogen suppresses oxytocin secretion
- ☐ E Estrone accounts for 80% of the estrogen produced during pregnancy

QUESTIONS 5–13

For each of the following questions, match the hormone with the description that best fits. Answer choices can be used once, more than once, or not at all.

- ☐ A hCG
- ☐ B hPL
- ☐ C Prolactin
- ☐ D Progesterone
- ☐ E Estriol

5. Suppresses maternal lymphocyte activity
6. Most sensitive marker for abnormal karyotype
7. Elevates ketone levels
8. Produced by the uterus
9. Inhibits lactation during pregnancy
10. Lack of this hormone can cause spontaneous abortion in the first trimester
11. Lack of this hormone is associated with an enzyme deficiency in the placenta
12. Elevated levels of this hormone are associated with twin pregnancy
13. Anencephaly causes lack of production of this hormone

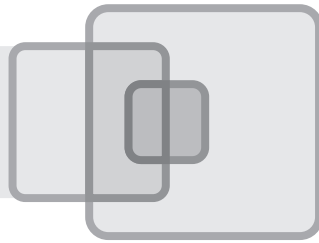


Answers and Explanations

1. **The answer is C** [I F 1 d]. Removing the corpus luteum at this early stage of pregnancy will have an adverse effect on the pregnancy because until 8 weeks of gestation the pregnancy is dependent on the production of progesterone from the corpus luteum for support. Progesterone supplementation should be initiated to support the pregnancy. At this gestation the hCG level no longer doubles every 2 days. The rate of rise slows. Having one ovary will not affect her hormonal production. Estrogen production from the corpus luteum will be affected since the corpus luteum has been removed.
2. **The correct answer is E** [I C 1 b, 4 b]. The clinical scenario (i.e., vaginal bleeding, early pregnancy-induced hypertension, enlarged uterus, and exaggerated β -hCG levels) is consistent with a molar pregnancy. Because of morphologic similarities between hCG and TSH (the α -subunit is homologous to TSH), hCG possesses TSH-like properties and can cause hyperthyroidism. The other endocrine glands are not affected by a molar pregnancy.
3. **The answer is D** [I C 3 c]. A high level of hCG in the second trimester is the most sensitive marker for Down syndrome. A high level of hCG in the first trimester is suggestive of molar pregnancy. hCG is part of the quadruple screen in the second trimester, not the first trimester. A low level of hCG is suggestive of ectopic pregnancy. hCG stimulates production of TSH, not TRH, leading to hyperthyroidism.
4. **The correct answer is B** [I G 1 a]. Estriol is produced primarily by the placenta. Estriol accounts for 80% of the estrogen produced during pregnancy. Anencephaly is associated with a decreased level of estriol. Estrogen increases oxytocin secretion to allow breastfeeding.

The answers are 5-D [I F 2 d], **6-A** [I C 3], **7-B** [I D 2 a], **8-C** [I E 1 a], **9-E** [I G 2 g], **10-D** [I F 1 c], **11-E** [I G 3 c], **12-A** [I C 4 b], and **13-E** [I G 3 b].

Progesterone suppresses production of maternal lymphocytic cytokines, which contribute to immune rejection of the fetus. Elevated hCG is the most sensitive serum marker for Down syndrome. hPL induces lipolysis, which provides energy for the mother in the form of fatty acids. hPL also provides energy for the fetus by elevating ketone levels. Prolactin is produced not only by the decidual tissue of the uterus, but also by the maternal and fetal pituitary glands. Lactation does not occur during pregnancy because estrogen inhibits the action of prolactin on the breast. Progesterone produced by the corpus luteum is essential for pregnancy maintenance until the eighth week of gestation. Progesterone suppositories are prescribed during the first 8 weeks of gestation in women with suspected corpus luteum deficiency. Low levels of estriol are associated with placental sulfatase deficiency. Abnormally high levels of hCG are seen in multiple gestations (twins). Anencephaly contributes to lack of ACTH production; therefore, the fetal adrenal cortex is not stimulated properly to convert pregnenolone to DHEA and DHEAS, which are essential in the production of estriol.



Fetal Physiology

EMMANUELLE PARÉ

I

INTRODUCTION

The normal growth and development of the fetus depends on the successful integration of the functions of the placenta, umbilical cord, amniotic fluid, and fetal organ systems.

II

PLACENTA

A Structure

1. Villi

- These structures, the functioning units of the placenta, are formed of invading placental tissue (**trophoblast**) and contain the **terminal fetal capillaries** of the umbilical arteries.
- The villi are surrounded by the **intervillous space** into which maternal blood from the **spiral arteries** (branches of the uterine arteries) is forced by maternal arterial pressure.
- Gases and nutrients pass **from the maternal blood** in the intervillous space, across the plasma membrane of the trophoblast to the basement membrane of the fetal capillary, and then through the single endothelial cell layer of the fetal capillary **to the fetal blood**. The fetal capillaries drain into the fetal veins that join to form the umbilical vein. Maternal blood drains from the intervillous space into the maternal veins.

- Placental cotyledons (lobes)** are formed from the branching villi supplied by one terminal arterial branch and its partner venous branch of the fetal umbilical vessels. About 15 to 30 cotyledons make up the fetal side of the placenta. The maternal side of the placenta is divided by septa into lobes (10 to 40 lobes).

B Function The placenta serves as the **interface** between the mother and the fetus. It transfers nutrition and oxygen from the mother to the fetus and removes carbon dioxide and other metabolic waste products from the fetus (to be eliminated by the mother). It also synthesizes proteins and hormones that support fetal development and important maternal physiologic changes.

1. Mother-to-fetus transfer of nutrients

- The essential substances for fetal growth and development move from the mother to the fetus in four ways:
 - (1) **Active transport:** amino acids and calcium
 - (2) **Facilitated transport:** glucose
 - (3) **Endocytosis:** cholesterol, insulin, iron, and immunoglobulin G (IgG)
 - (4) **Sodium pumps and chloride channels:** ions
- Solute size and lipid solubility are also important factors that influence transport.

2. Gas exchange

- This process involves supplying oxygen to the fetus and removing carbon dioxide from the fetus.
- These exchanges are achieved through **passive diffusion** and their flux is dependent on the concentration gradients across the membrane.

3. Secretion of proteins and steroid hormones (see Chapter 1)

- Progesterone** is produced by the placenta from maternal cholesterol, is secreted into the maternal circulation, and is important for maintaining pregnancy.

- b. **Estrogen** is converted from circulating fetal androgens (dehydroepiandrosterone sulfate [DHAS]) supplied by the maternal and fetal adrenal glands. Estrogen plays an important role in maternal physiologic changes in pregnancy, labor, and lactation.
 - c. Numerous **proteins, peptides, and growth factors** are produced in the placenta. They are important for placental growth, fetal growth and development, and the maternal physiologic changes necessary to ensure adequate nutrition to the fetus.
4. **Immunology.** Invading placental cells express a unique antigen, HLA-G, which is not recognized as a “foreign” antigen by the mother. Other unique antigens and local immune suppression contribute to the prevention of rejection of the fetal–placental unit.

C Metabolism Glucose is the primary substrate for placental **aerobic** metabolism.

III

UMBILICAL CORD

A Umbilical arteries Two umbilical arteries originate from the fetal aorta. They supply fetal blood to all portions of the placenta for gas, solute, and nutrients exchange. Contrary to what is seen in the neonatal and adult circulations, the umbilical arteries carry **deoxygenated blood** to the placenta. A single umbilical artery is associated with intrauterine growth restriction and congenital anomalies (cardiac and renal) in some infants.

B Umbilical vein One umbilical vein returns **nutrient-rich, oxygen-rich blood** to the fetus.

IV

AMNIOTIC MEMBRANES AND FLUID

A Membranes

1. **Amnion.** The amnion is a single layer of epithelial cells surrounding the fetus and containing the amniotic fluid.
2. **Chorion.** The chorion, which lies adjacent to the uterine endometrium, is exterior and fused to the amnion.

B Fluid

1. **Fetal lung fluid** appears to be important for the successful development of the bronchial tree, but most of the amniotic fluid volume derives primarily from the **fetal urine**. Amniotic fluid during the second trimester is crucial for fetal lung development.
2. Early in gestation, the fluid surrounding the embryo is believed to be transudative. By the second trimester, the fetal lungs and primarily the kidneys produce the amniotic fluid. Fluid resorption results primarily from fetal swallowing, and also from flow across the amnion or the chorion to the fetal or maternal vessels. Fluid volume increases with increasing the gestational age until the middle of the third trimester, after which the volume stays stable and may decrease somewhat at term.

V

FETUS

A Metabolism Fetal metabolism is primarily **oxidative**. Normal metabolism is necessary to maintain the normal function of existing tissue and to support the acquisition of new tissue.

1. Requirements

- a. **Glucose.** The principal sugar in fetal blood is **glucose**; it is a major nutrient for growth and energy in the fetus. The maternal blood (via the placenta) is the source of fetal glucose, and the fetal glucose level is determined by the maternal level.
 - b. **Oxygen.** Fetal oxygen consumption is approximately **8 mL/kg/min** compared to an adult oxygen consumption of about 3 mL/kg/min.
 - c. **Amino acids.** The fetus synthesizes protein from amino acids from maternal blood.
2. **Hormones important for fetal growth.** Hormones produced in the fetus, placenta, and mother function together to promote the growth and development of the fetus.
- a. **Human placental lactogen (hPL) or human chorionic somatomammotropin (hCS).** This maternal hormone increases **resistance to insulin** and blocks the peripheral uptake and use

of glucose by maternal tissues, raising the maternal blood glucose concentration to favor placental transfer of glucose to the fetus.

b. Insulin. The fetus produces its own insulin.

c. Insulin-like growth factors I and II, human placental growth hormone, and other growth factors. Growth factors produced in the placenta are responsible for the regulation of cell proliferation and cell differentiation in the fetus.

B Organ systems

1. Cardiovascular

a. Unique features of the fetal circulation (Fig. 2–1)

- (1) **Umbilical vein.** The umbilical vein carries **oxygenated, nutrient-rich** blood from the placenta to the fetus. The umbilical vein gives off branches to the liver and becomes the **ductus venosus**.
- (2) **Ductus venosus.** The ductus venosus carries at least half of the umbilical vein blood flow, and brings oxygenated blood from the placenta to the inferior vena cava. Blood from the

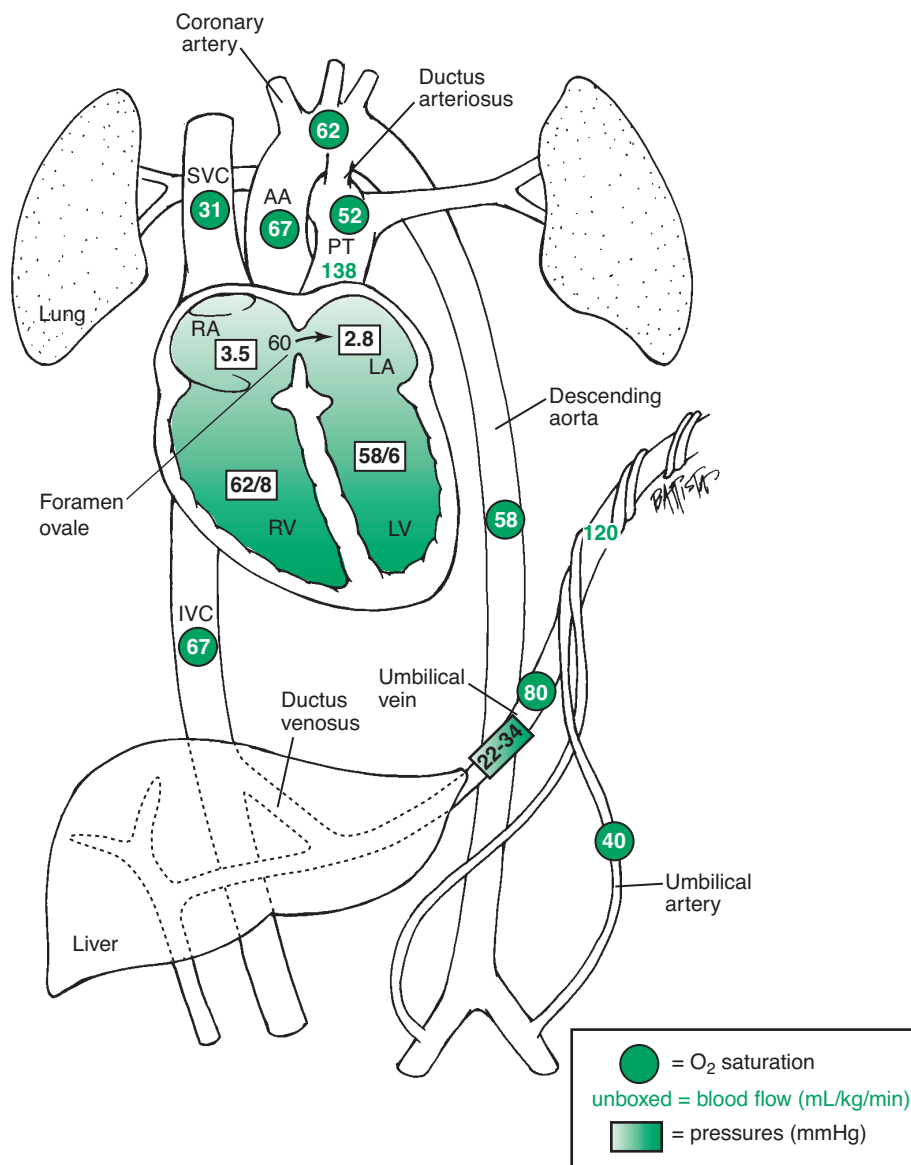


FIGURE 2–1 Hemodynamics of the fetus (in utero). AA, ascending aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PT, pulmonary trunk; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

portal vein flows into the ductus venosus, thereby decreasing the overall oxygen content of the blood entering the inferior vena cava. Thus, blood flowing into the right ventricle is not as well oxygenated as blood coming directly from the placenta.

- (3) **Foramen ovale.** The foramen ovale is a right-to-left intracardiac (atrial) shunt. Well-oxygenated blood carried by the inferior vena cava from the ductus venosus streams preferentially from the right atrium to the left atrium across the **foramen ovale** and then to the left ventricle, brain, and upper body. Less oxygenated blood returning from the systemic circulation also forms a stream in the inferior vena cava that joins blood from the superior vena cava to flow preferentially across the tricuspid valve to the right ventricle.
 - (4) **Ductus arteriosus.** Blood returning from the systemic circulation (less oxygenated) is delivered preferentially to the right ventricle. From the right ventricle, blood flows into the pulmonary artery, then through the **ductus arteriosus** to the descending aorta to the systemic circulation and umbilical arteries. The ductus arteriosus connects the left pulmonary artery to the arch of the aorta.
 - (a) The **high vascular resistance in the fetal lungs** is greater than the aortic pressure, which diverts blood away from the lungs and into the ductus arteriosus and the aorta. The umbilical arteries deliver the blood from the aorta to the placenta for gas exchange.
 - (b) Prostaglandins, such as prostaglandin E, play a role in maintaining patency of the ductus arteriosus. Prostaglandin inhibitors promote closure of the ductus.
 - b. Circulatory adjustments to neonatal life.** At birth, the lungs expand and the pulmonary vascular resistance decreases, which dramatically increases the pulmonary blood flow. Constriction then closure of the ductus arteriosus, also increases pulmonary blood flow. The right atrial pressure decreases and the left atrial pressure increases which leads to the physiologic closure of the foramen ovale. The ductus arteriosus, ductus venosus, and umbilical vein are no longer patent and become known as the ligamentum arteriosum, ligamentum venosum, and ligamentum teres, respectively. The intra-abdominal portion of the umbilical arteries becomes the lateral umbilical ligaments.
 - c. Heart rate and cardiac output.** Cardiac output of the fetal heart is estimated to be **300 mL/kg/min**, which is higher than the cardiac output of the adult (about 70 mL/kg/min). The cardiac output of the right ventricle is greater than that of the left ventricle (60% vs. 40%), resulting in a right ventricular dominance. The normal fetal heart rate is 120 to 160 beats/min, and the average fetal heart rate slowly decreases with increasing gestational age.
 - d. Regulation of blood flow and pressures.** The cardiovascular system is controlled by a complex integration of autonomic and hormonal effects. The stimulation of baroreceptors (by changes in blood flow) and chemoreceptors (by changes in oxygenation) is responsible for the initiation of autonomic reflexes and the secretion of hormones to coordinate the regulation of blood flow, pressure, and heart rate in the fetus.
- 2. Respiratory**
- a.** The fetal lungs play no role in gas exchange. Oxygen and carbon dioxide are exchanged between fetal and maternal blood across the placenta. The partial pressure of oxygen in intervillous blood is lower in the fetus compared with the mother, which favorably influences the transfer of oxygen from maternal to fetal blood. Similarly, physiologic maternal respiratory changes result in a lower partial pressure of carbon dioxide in the maternal circulation, which favors the transfer of carbon dioxide from the fetus to the mother.
 - b.** At about 34 weeks of gestation, the fetal lungs produce **surfactant**, a combination of phospholipids mainly, lipids and proteins from the type II pneumocytes. Surfactant is essential for successful respiration because it lowers the surface tension in the alveoli to prevent alveolar collapse.
- 3. Gastrointestinal/hepatic**
- a.** Fetal **swallowing** of the amniotic fluid is potentially another source of nutrients as the amniotic fluid contains glucose, lactate and amino acids. The fetal intestine absorbs water from the swallowed amniotic fluid.
 - b. Meconium** is composed of intestinal tract secretions and desquamation of intestinal epithelial cells.

- c. The fetal liver is the major source of fetal cholesterol.
 - d. The majority of unconjugated bilirubin is removed from the fetal circulation by the placenta, where it is transferred to the maternal circulation, conjugated by the maternal liver, and excreted. At term, fetal hepatic conjugation of bilirubin is relatively deficient, and a mild **hyperbilirubinemia** may be seen in the term neonate in the first few days of life.
4. **Renal**
- a. Fetal urine production begins toward the end of the first trimester and is essential for maintaining amniotic fluid volume as gestation advances.
 - b. Fetal urine is **hypotonic**.
 - c. Most water and electrolytes exchange occurs in the placenta.
5. **Hematologic**
- a. **Hematopoiesis** occurs in the yolk sac in the second week of gestation, in the liver and spleen in the fifth week of gestation, and in the bone marrow by the 11th week of gestation.
 - b. **Hemoglobin**
 - (1) The hemoglobin concentration is high in the term fetus (16 to 18 g/dL) compared to that in the mother.
 - (2) **Fetal hemoglobin** is composed of two α -globin and two γ -globin chains. It differs from adult hemoglobin, which is composed of two α -globin and two β -globin chains.
 - (3) Adult hemoglobin can be found in the fetus as early as 12 weeks' gestation and its level increases during the third trimester. However, at term, 70% of the circulating hemoglobin remains fetal hemoglobin.
 - (4) Fetal hemoglobin has a **high affinity for oxygen**, resulting in an oxygen dissociation curve that is **shifted to the left** compared with that in adults (Fig. 2–2). Because of the high affinity of fetal hemoglobin for oxygen, fetal red blood cells efficiently extract oxygen from the maternal blood in the placenta.
 - c. Erythropoietin originates in the fetal liver and is highest in utero.
6. **Endocrine** (see Chapter 1)
- a. **Thyroid gland.** Adequate levels of thyroxine are important for normal neurologic development. The fetal thyroid starts to be functional at the end of the first trimester and fetal thyroxine levels steadily increase from midgestation until term.
 - b. **Adrenal gland.** DHAS is secreted by the fetal zone of the adrenal in response to stimulation by adrenocorticotrophic hormone (ACTH) and human chorionic gonadotropin (hCG). The fetal adrenal gland also produces cortisol and catecholamines.

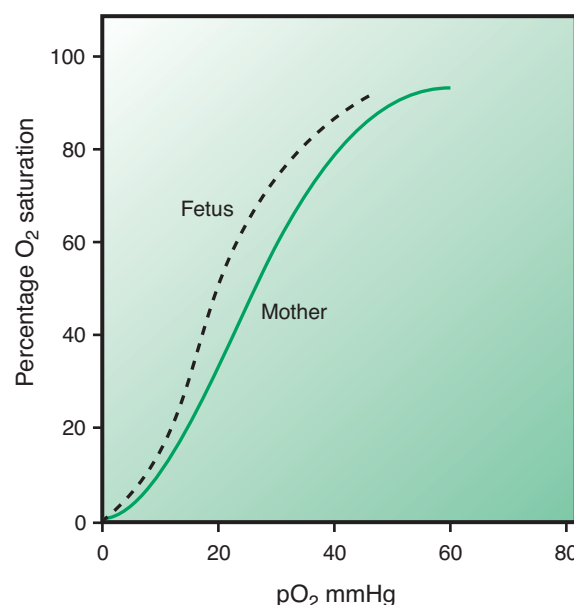
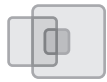


FIGURE 2–2 Comparison of the fetal and maternal hemoglobin dissociation curves. (Redrawn from Gabbe SG. *Obstetrics: Normal and Problem Pregnancies*. 4th Ed. New York: Churchill Livingstone, 2002:49).

C Immune system

1. Although the fetus produces macrophages and granulocytes, the cellular immunity of the fetus and neonate is not as active or efficient as adult cellular immunity. Similarly, the fetus cannot mount adult-level antibody responses to antigen stimulation.
2. In response to infection, **fetal IgM** increases. In the absence of infection, fetal levels of IgA and IgM are much lower than adult levels.
3. The majority of immunoglobulin found in the fetus is IgG and is due to transplacental passage from the mother. IgG is the only immunoglobulin isotype that crosses the placenta.



Study Questions for Chapter 2

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. Which vessels lead *into* and *out* of the ductus venosus, respectively?
 - ☐ A Pulmonary artery; aorta
 - ☐ B Inferior vena cava; portal vein
 - ☐ C Umbilical artery; portal vein
 - ☐ D Umbilical vein; inferior vena cava
 - ☐ E Right atrium; left atrium

2. A 37-year-old woman, gravida 1, para 1, just delivered at term a male infant weighing 3,980 g with APGARs of 9 and 9 at 1 and 5 minutes, respectively. Delivery was via spontaneous vaginal delivery without any complications. After clamping of the umbilical cord, the baby takes his first breath. Which event(s) is/are directly responsible for the most efficient oxygenation of blood inside the lungs?
 - ☐ A Closure of foramen ovale
 - ☐ B Closure of ductus arteriosus
 - ☐ C Closure of foramen ovale and ductus arteriosus
 - ☐ D Closure of umbilical vein and artery
 - ☐ E Closure of ligamentum arteriosum and ligamentum teres

3. Two medical students are discussing fetal oxygen consumption and fetal cardiac output. The first student claims that the fetal cardiac output is at least two times that of the adult cardiac output. The second student claims that the fetal oxygen consumption is probably half of adult oxygen consumption. The cardiac output and oxygen consumption in a fetus are approximately what multiple/fraction of that compared with an adult, respectively?
 - ☐ A 2; 2
 - ☐ B 4; 3
 - ☐ C 1/2; 1/2
 - ☐ D 1/3; 3
 - ☐ E 4; 1/2

4. The most oxygenated blood is found in which part of the fetal circulation?
 - ☐ A Ductus venosus
 - ☐ B Portal vein
 - ☐ C Inferior vena cava
 - ☐ D Ductus arteriosus
 - ☐ E Descending aorta

QUESTIONS 5–8

For each substance listed below, select its route of transfer across the placenta. Each answer choice may be used once, more than once, or not at all.

- ☐ A Endocytosis
- ☐ B Facilitated transport
- ☐ C Passive diffusion
- ☐ D Active transport
- ☐ E Ion pumps

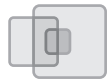
5. Glucose
6. Iron
7. Amino acids
8. Carbon dioxide

QUESTIONS 9–13

For each statement below, match the period of fetal/early neonatal life during which the event occurs. Each answer can be used once, more than once, or not at all.

- ☐ A First trimester
- ☐ B Second trimester
- ☐ C Third trimester
- ☐ D Postnatal

9. Highest concentration of hemoglobin containing two α -globin and two β -globin chains
10. Amniotic fluid volume derived from transudation
11. Closure of the ductus arteriosus
12. Significant amniotic fluid volume contribution from the lungs
13. Production of red blood cells by the spleen



Answers and Explanations

1. The answer is D [V B 1 a (2), 1 a (3)]. The umbilical vein gives off branches to the liver and becomes the ductus venosus. The ductus venosus carries at least half of the umbilical vein blood flow, and brings oxygenated blood from the placenta to the inferior vena cava. The foramen ovale is a right-to-left intracardiac (atrial) shunt. Well-oxygenated blood carried by the inferior vena cava from the ductus venosus streams preferentially from the right atrium to the left atrium across the foramen ovale and then to the left ventricle, brain, and upper body. Less oxygenated blood returning from the systemic circulation also forms a stream in the inferior vena cava that joins blood from the superior vena cava to flow preferentially across the tricuspid valve to the right ventricle. Blood returning from the systemic circulation (less oxygenated) is delivered preferentially to the right ventricle. From the right ventricle, blood flows into the pulmonary artery, then through the ductus arteriosus to the descending aorta to the systemic circulation and umbilical arteries. The ductus arteriosus connects the left pulmonary artery to the arch of the aorta. The high vascular resistance in the fetal lungs is greater than the aortic pressure, which diverts blood away from the lungs and into the ductus arteriosus and the aorta. The umbilical arteries deliver the blood from the aorta to the placenta for gas exchange.

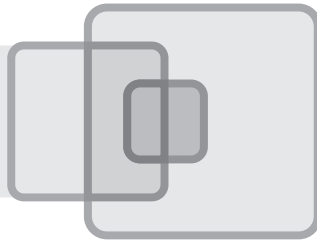
2. The answer is C [V B 1 b]. When the baby takes his first breath, resistance in the pulmonary vessel circuit is substantially reduced, and thus blood can flow through the pulmonary artery to the lungs (instead of to the aorta through the ductus arteriosus) to become oxygenated. This event also decreases the pressure in the right atrium, allowing closure of the foramen ovale. Both of these events are necessary for the most efficient oxygenation of blood (closure of the foramen ovale allows all of the blood returning to the heart to be oxygenated). Conditions such as atrial septal defect (ASD) do not allow for the most efficient oxygenation of blood returning to the heart because a small percentage of that deoxygenated blood is shunted to the left atrium and into systemic circulation instead of into the lungs to become oxygenated. The ligamentum arteriosum is the closed (nonpatent) ductus arteriosus, and the ligamentum teres is the closed (nonpatent) umbilical vein.

3. The answer is B [V A 1 b and V B 1 c]. Fetal cardiac output is approximately 300 mL/kg/min, whereas an average adult's cardiac output is 70 mL/kg/min. Fetal oxygen consumption is approximately 8 mL/kg/min, whereas adult oxygen consumption is approximately 3 mL/kg/min.

4. The answer is A [V B 1 a (2)]. The umbilical vein carries the most well-oxygenated blood from the placenta. The ductus venosus carries slightly less oxygen because it mixes with the portal venous blood. The inferior vena cava carries blood from both the ductus venosus and the systemic circulation; it therefore carries less oxygen overall than the ductus venosus. The ductus arteriosus and descending aorta receive blood returning from the systemic circulation and therefore have less oxygen than the other choices.

The answers are 5-B [II B 1 a (2)], **6-A** [II B 1 a (3)], **7-D** [II B 1 a (1)], and **8-C** [II B 2]. Glucose is transported across the placenta via facilitated transport. Iron is transported via endocytosis. Amino acids are transported via active transport. Carbon dioxide passively diffuses across the placenta.

The answers are 9-C [V B 5 b (2)], **10-A** [IV B 2], **11-D** [V B 1 b], **12-B** [IV B], and **13-A** [V B 5 a]. The highest concentration of adult hemoglobin is near term. However, even near term, fetal hemoglobin makes up the majority of circulating hemoglobin (almost 70%). Amniotic fluid is a transudate during early pregnancy. Immediately after birth, constriction then closure of the ductus arteriosus, also increases pulmonary blood flow. The ductus arteriosus is no longer patent and becomes known as the ligamentum arteriosum. In the second trimester, the lungs and the kidneys both contribute to amniotic fluid volume. The contribution of the kidneys steadily increases until it is the major contributor of amniotic fluid volume by the end of the second trimester and in the third trimester. Hematopoiesis occurs in the yolk sac in the second week of gestation, in the liver and spleen in the fifth week of gestation, and in the bone marrow by the 11th week of gestation.



Normal Pregnancy, the Puerperium, and Lactation

PETER CHEN

I

DIAGNOSIS OF PREGNANCY

A Presumptive symptoms

1. **Amenorrhea.** Amenorrhea, or the abrupt cessation of spontaneous, cyclic, and predictable menstruation, is strongly suggestive of pregnancy. Because ovulation can be late in any given cycle, the menses should be **at least 10 days late** before their absence is considered a reliable indication.
2. **Breast changes.** In very early pregnancy, women report tenderness and tingling in the breasts. Breast enlargement and nodularity are evident as early as the second month of pregnancy. The nipples and areolae enlarge and become more deeply pigmented.
3. **Nausea (with or without vomiting).** The so-called **morning sickness of pregnancy** usually begins early in the day and lasts for several hours, although occasionally it persists longer and may occur at other times. Gastrointestinal disturbances begin at 4 to 6 weeks' gestation and usually last no longer than the first trimester. Excessive nausea and vomiting (i.e., **hyperemesis gravidarum**) can result in dehydration, weight loss, electrolyte imbalance, and the need for hospitalization; intravenous hyperalimentation may be indicated in severe cases.
4. **Disturbances in urination.** Early in pregnancy, the enlarging uterus puts pressure on the bladder, causing **frequent urination**. This condition improves as the uterus grows and moves up into the abdomen, but returns late in pregnancy when the fetal head settles into the pelvis against the bladder.
5. **Fatigue.** Tiredness is one of the earliest symptoms of pregnancy. Fatigue usually persists into the second trimester; the need for sleep returns to normal by the 16th to 18th week.
6. **Sensation of fetal movement.** Between the 16th and 20th week after the last menstrual period (LMP), a woman begins to feel movement in the lower abdomen, described as a fluttering or gas bubbles. This is known as **quickening**.

B Clinical evidence

1. **Enlargement of the abdomen.** By the end of the 12th week of pregnancy, the uterus can be felt above the symphysis pubis. By the 20th week, the uterus should be at the level of the umbilicus. Between the 20th and 37th week, the fundal height in centimeters should correspond, within 2 cm, to the gestational age in weeks (Fig. 3-1).
2. **Uterine and cervical changes.** The uterus enlarges and softens early in pregnancy (at approximately 6 weeks' gestation), and lateral uterine vessel pulsations are palpable on vaginal examination. The softening between the cervix and the uterine fundus causes a sensation of separateness between these two structures (**Hegar's sign**). The vaginal mucosa has a bluish color within the first 6 to 8 weeks of pregnancy (**Chadwick's sign**).
3. **Endocrine tests for pregnancy.** These tests depend on **human chorionic gonadotropin (hCG)** levels in maternal plasma and excretion of hCG in the urine, which are identified by a number of immunoassays and bioassays. The presence of hCG can be demonstrated in maternal plasma by 8 to 9 days after ovulation.

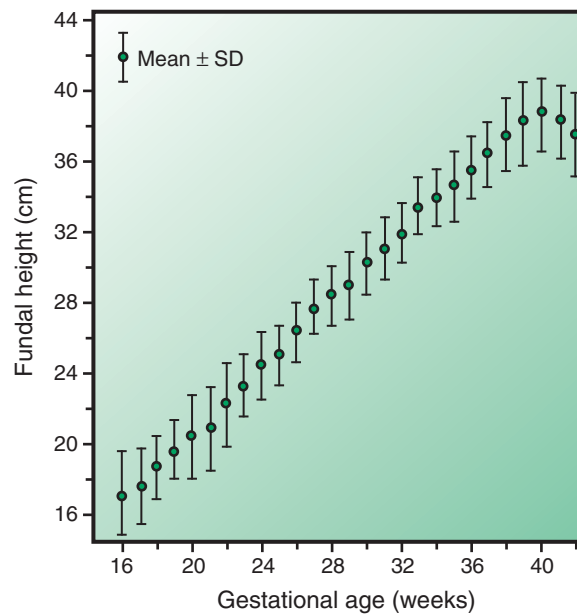


FIGURE 3-1 Fundal height versus gestational age. (Reprinted with permission from Gabbe SG. *Obstetrics: Normal and Problem Pregnancies*. 3rd Ed. New York: Churchill Livingstone, 1996:181).

- a. **Urine pregnancy tests** detect the presence of hCG. This depends on the recognition of hCG or its β -subunit by an antibody to the hCG molecule or the β -subunit.
- b. **Serum pregnancy tests** detect the presence and quantify the β -subunit of hCG, thus allowing serial determinations to observe increases and decreases in the level of hCG. The serum test is more sensitive than the urine test.

C Confirming the diagnosis of pregnancy

1. **Identification of a heartbeat.** The diagnosis of pregnancy is confirmed with the identification of the fetal heartbeat, which ranges from 120 to 160 beats/min. The fetal heart can be identified by the 10th week with an ultrasonic fetal heart Doppler monitor and at 17 to 19 weeks by auscultation with a stethoscope.
2. **Ultrasonographic recognition of the fetus**
 - a. After 5 weeks of amenorrhea, an early **chorionic (gestational) sac** is visible as a small, fluid-filled structure surrounded by an echogenic rim of tissue on transvaginal ultrasound. The **embryo** is apparent within the gestational sac after 6 weeks of amenorrhea.
 - b. **Fetal heart activity** is seen by real-time ultrasonography after 6 weeks of gestation. The normal heart rate may be as low as 90 beats/min at 6 weeks and increases during the first trimester.

- ### **D** Pregnancy dating
- The **estimated date of confinement (EDC)**, or due date, is based on the assumption that a woman has a 28-day cycle, with ovulation on Day 14 or 15. Pregnancy lasts for 280 days (40 weeks) from the LMP. The EDC is therefore 9 calendar months plus 7 days from the start of the LMP; it is customary to estimate the **EDC** by counting back 3 calendar months and adding 7 days to the LMP (**Naegle's rule**). Because ovulation does not always occur at midcycle (the postovulatory phase in any cycle lasts for 14 days), the EDC must be adjusted accordingly. For example, ovulation in a woman with a 35-day cycle occurs on approximately Day 21; therefore, the EDC in such a woman is later than that predicted by the Naegle's rule (see Chapter 6 regarding ultrasound dating).

II

PREGNANCY

- #### **A** First trimester
- This period extends from the LMP through the first 12 to 13 weeks of pregnancy.

1. **Signs and symptoms**
 - a. Nausea
 - b. Fatigue

- c. Breast tenderness
 - d. Frequent urination
 - e. Minimal abdominal enlargement (the uterus is still in the pelvis)
2. Bleeding occurs in the first trimester of approximately 25% of all pregnancies; spontaneous abortion occurs in 25% to 50% of these pregnancies. Uterine cramping with bleeding in the first trimester is more suggestive of impending abortion than either bleeding or cramping alone.

B Second trimester This period extends from 14 weeks of pregnancy through 27 weeks of pregnancy.

1. **Signs and symptoms**

- a. **General well-being.** The second trimester is often the most comfortable time for a pregnant woman because the symptoms of the first trimester have disappeared, and the discomfort of the last trimester is not yet present.
 - b. **Pain.** As the uterus grows, a certain amount of pulling and stretching of pelvic structures occurs. Round ligament pain, which results from the stretching of the round ligaments that are attached to the top of the uterus on each side and the corresponding lateral pelvic wall, is common.
 - c. **Contractions.** Palpable uterine contractions (**Braxton Hicks contractions**) that are mild and irregular can begin during the second trimester.
2. **Bleeding.** A low-lying placenta that causes bleeding at this stage usually moves away from the cervix as the uterus grows.
3. **Fetus.** The fetus attains a size of almost 1,000 g (more than 2 lb) by the 28th week.
- a. **Motion.** Quickening (see I A 6) begins between the 16th and 20th week.
 - b. **Viability.** Infants born at the end of the second trimester have an 80% to 90% chance of survival. If death occurs, it is usually from respiratory distress due to lung immaturity.
4. **Complications of second-trimester pregnancies** include an incompetent cervix (i.e., painless dilation of the cervix in the second trimester). Resulting conditions include:
- a. **Premature rupture of the membranes** (PROM) can occur without labor or with an incompetent cervix and can result in serious bacterial infections in both the mother and the fetus.
 - b. **Premature labor** can occur without an incompetent cervix. When dilation or effacement of the cervix occurs, tocolytic agents are necessary to prevent delivery (see Chapter 15).

C Third trimester This period extends from 28 weeks of pregnancy until term, or 40 weeks' gestation.

1. **Symptoms**

- a. **Braxton Hicks contractions** (see II B 1 c) become more apparent in the third trimester.
- b. **Pain in the lower back and legs** is often caused by pressure on muscles and nerves by the uterus and fetal head, which fills the pelvis at this time.
- c. **Lightening** is the descent of the fetal head to or even through the pelvic inlet due to the development of a well-formed lower uterine segment and a reduction in the volume of amniotic fluid.

2. **Fetus**

- a. **Weight.** The fetus gains weight at a rate of approximately 224 g (0.5 lb) per week for the last 4 weeks and weighs an average of 3,300 g (7.0 to 7.5 lb) at term.
- b. **Motion**
 - (1) A decrease in fetal motion usually occurs because of the size of the fetus and lack of room within the uterus. However, some decreased fetal activity may indicate fetal compromise due to uteroplacental insufficiency.
 - (2) The fetal mortality rate decreases from 44/1,000 to 10/1,000 as measured by a fetal movement screening method. (This commonly used method [daily fetal kick count] requires maternal perceptions of at least ten fetal movements in 2 hours daily in the third trimester.)

3. **Bleeding**

- a. **Bloody show**, a discharge of a combination of blood and mucus caused by thinning and stretching of the cervix, is a sure sign of the approach of labor.
- b. **Heavy bleeding** suggests a more serious condition such as **placenta previa** (the placenta developing in the lower uterine segment and completely or partially covering the internal os, usually **painless** bleeding) or **abruptio placentae** (premature separation of the normally implanted placenta, usually **painful** bleeding) (see Chapter 9).

4. **Rupture of membranes** is either a sudden gush or a slow leak of amniotic fluid that can happen at any time without warning.
 - a. **Brownish or greenish fluid** may represent meconium staining of the fluid, the sign of a **fetal bowel movement** that may or may not represent fetal stress.
 - b. At term, **labor** usually begins within 24 hours after rupture of membranes.
 - c. At term, **induction of labor** is indicated if there is no labor within 6 to 24 hours of rupture or if there is any evidence of infection (**chorioamnionitis**).
5. **Labor.** Contractions that occur at decreasing intervals with increasing intensity cause the progressive dilation and effacement of the cervix.

III

STATUS OF THE FETUS

A Growth and development

1. **Weight.** A normal fetus weighs approximately 1,000 g (more than 2 lb) at 26 to 28 weeks, 2,500 g (5.5 lb) at 36 weeks, and 3,300 g (7.0 to 7.5 lb) at 40 weeks.
2. **Lung maturity.** Fetal lung maturity can be assessed by measuring surface-active lipid components of surfactant (e.g., lecithin and phosphatidylglycerol), which are secreted by the type II pneumocytes of fetal lung alveoli. Fetal lung maturity is essential for normal respiration immediately after birth. These measurements are made by laboratory examination of **amniotic fluid**.
 - a. **Lecithin-to-sphingomyelin (L/S) ratio.** Studies have shown that when the level of lecithin in amniotic fluid increases to at least **twice** that of sphingomyelin (at approximately 35 weeks), the risk of respiratory distress is very low (Fig. 3–2).
 - b. **Phosphatidylglycerol.** The presence of phosphatidylglycerol in the amniotic fluid provides even more definite assurance of lung maturity.
 - c. **Respiratory distress syndrome (RDS).** Infants born before phosphatidylglycerol appears in surfactant, even with an L/S ratio of 2:1, may be at risk for RDS.
 - d. **Early fetal lung maturation** (32 to 35 weeks) is seen with maternal hypertension, PROM, and intrauterine growth retardation, all of which are stressful to the fetus. This stress increases **fetal cortisol secretion**, which in turn accelerates fetal lung maturation.

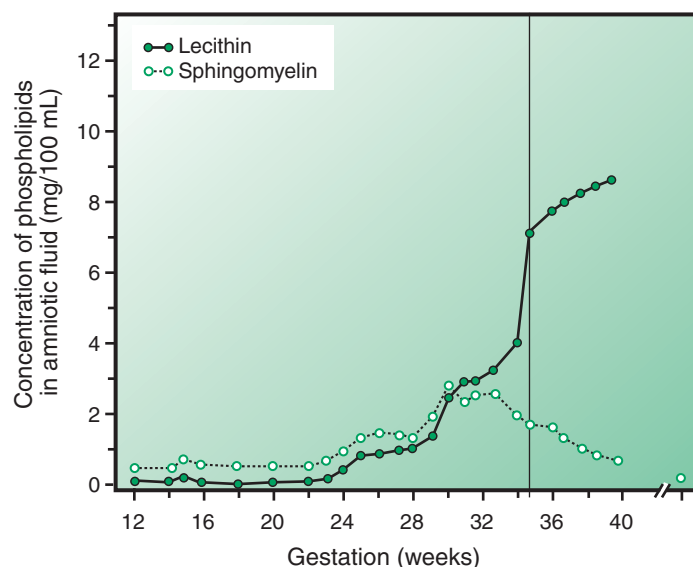


FIGURE 3–2 Changes in mean concentrations of lecithin and sphingomyelin in amniotic fluid during gestation in normal pregnancy. (Reprinted with permission from Cunningham FG, MacDonald PC, Gant NF, et al. *Williams Obstetrics*. 20th Ed. New York: McGraw-Hill, 1997:970, Figure 42–2).

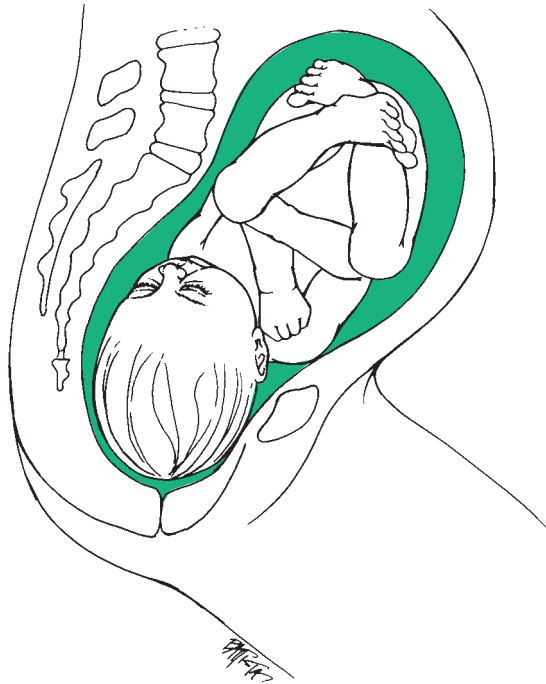


FIGURE 3–3 Vertex presentation. (Redrawn from Cunningham FG, MacDonald PC, Gant NF, et al. *Williams Obstetrics*. 20th Ed. New York: McGraw-Hill, 1997:320, Figure 12–1 #2).

e. Glucocorticoids. Administration of glucocorticoids to mothers between the 24th and 34th week of pregnancy effects an increase in the rate of maturation of the human fetal lung and is associated with a reduced rate of respiratory distress in their prematurely born infants.

B Lie of the fetus is the relation of the long axis of the fetus to the long axis of the mother and is either longitudinal or transverse.

1. **Longitudinal lie.** In most labors (more than 99%) at term, the fetal head is either up or down in a longitudinal lie.
2. **Transverse lie.** The fetus is crosswise in the uterus in a transverse lie.
3. **Oblique lie.** This indicates an unstable situation that becomes either a longitudinal or transverse lie during the course of labor.

C Fetal presentation is determined by the portion of the fetus that can be felt through the cervix.

1. **Cephalic presentations** are classified according to the position of the fetal head in relation to the body of the fetus.
 - a. **Vertex.** The head is flexed so that the chin is in contact with the chest, and the occiput of the fetal head presents. A vertex presentation occurs in 95% of all cephalic presentations (Fig. 3–3).
 - b. **Face.** The neck is extended sharply so that the occiput and the back of the fetus are touching, and the face is the presenting part (Fig. 3–4).
 - c. **Brow.** The fetal head is extended partially but converts into a vertex or face presentation during labor (Fig. 3–5).
2. **Breech presentations** are classified according to the position of the legs and buttocks, which present first. Breech presentations occur in 3.5% of all pregnancies (Fig. 3–6).
 - a. In a **complete breech**, both the legs and the hips are flexed.
 - b. In an **incomplete breech**, one hip is not flexed, and one foot or one knee lies below the breech (i.e., one foot or one knee is lowermost in the birth canal).
 - c. In a **frank breech**, the hips are flexed and the legs are extended.

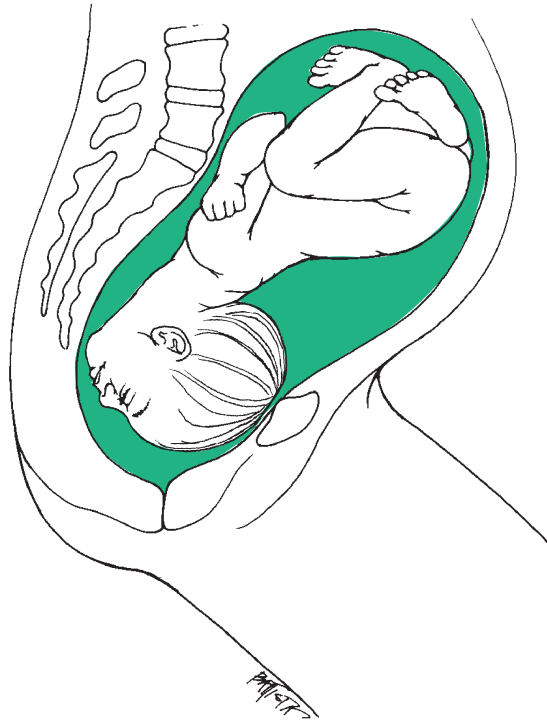


FIGURE 3–4 Face presentation. (Redrawn from Gabbe SG. *Obstetrics: Normal and Problem Pregnancies*. 3rd Ed. New York: Churchill Livingstone, 1996:473, Figure 16–9).

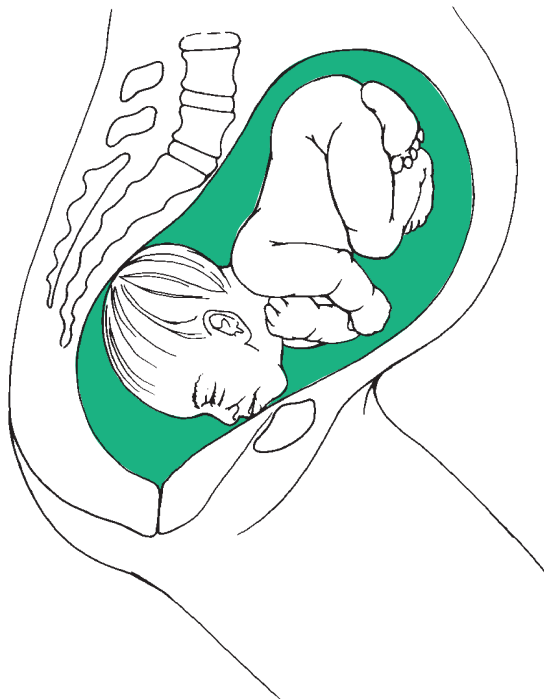


FIGURE 3–5 Brow presentation. (Redrawn from Gabbe SG. *Obstetrics: Normal and Problem Pregnancies*. 3rd Ed. New York: Churchill Livingstone, 1996:475, Figure 16–10).



FIGURE 3–6 Breech presentation. (Reprinted with permission from Gabbe SG. *Obstetrics: Normal and Problem Pregnancies*. 3rd Ed. New York: Churchill Livingstone, 1996:479, Figure 16–14).

IV

PUERPERIUM

This period of 4 to 6 weeks starts immediately after delivery and ends when the reproductive tract has returned to its nonpregnant condition. Multiple anatomic and physiologic changes occur during this time, and the potential exists for significant complications, such as infection or hemorrhage.

A Physiology

1. **Involution of the uterus.** The uterus regains its usual nonpregnant size within 5 to 6 weeks, shrinking from 1,000 g immediately postpartum to 100 g. This rapid atrophy occurs because of the marked decrease in the size of the muscle cells rather than the decrease in their total number. Breastfeeding accelerates involution of the uterus because stimulation of the nipples releases oxytocin from the neurohypophysis; the resulting contractions of the myometrium facilitate the involution of the uterus.
 - a. **Afterpains.** The uterus contracts throughout the period of involution, which produces afterpains, especially in multiparous women and nursing mothers. In primiparous women, the uterus tends to remain contracted tonically, whereas in multiparous women, the uterus contracts vigorously at intervals.
 - b. **Lochia.** This uterine discharge follows delivery and lasts for 3 or 4 weeks. Foul-smelling lochia suggests infection.
 - (1) **Lochia rubra.** This blood-stained fluid lasts for the first few days.
 - (2) **Lochia serosa.** This discharge appears 3 to 4 days after delivery. It is paler than lochia rubra because it is admixed with serum.
 - (3) **Lochia alba.** After the 10th day, because of an admixture with leukocytes, the lochia assumes a white or yellow-white color.
2. **Involutorial changes of the renal system.** The puerperal bladder has an increased capacity and a relative insensitivity to intravesical fluid pressure.
 - a. **Incomplete emptying,** resulting in excessive residual urine, and overdistension may lead to a postpartum urinary tract infection.
 - b. **Diuresis** usually occurs between the second and fifth postpartum day.
 - c. **Anatomic changes,** such as the dilation of the calyces, renal pelvis, and ureters, that are characteristic of pregnancy may persist as long as 8 weeks postpartum. Functionally, the increased renal plasma flow, glomerular filtration rate, and creatinine clearance rate associated with pregnancy return to normal by 6 weeks after delivery.

3. **Cardiovascular changes.** The changes that occurred during pregnancy (e.g., increases in heart rate, cardiac output, and blood volume) generally return to baseline by approximately 6 weeks' postpartum. Peripheral vascular resistance also returns to the prepregnancy level by this time. Most of these parameters return to normal within the first 2 weeks' postpartum.
4. **Blood.** A marked **leukocytosis** occurs during and after labor. The leukocytosis, primarily a demargination event of granulocytosis, may be as high as 30,000/mm³. Pregnancy-induced changes in **blood coagulation factors** persist for variable periods of time after delivery. Elevated plasma fibrinogen levels are maintained at least through the first week of the puerperium.
5. **Ovulation and menstruation**
 - a. **Nonlactating women.** The first menstrual flow usually returns within 6 to 8 weeks after delivery, with ovulation occurring at 2 to 4 weeks' postpartum.
 - b. **Lactating women.** Ovulation is much less frequent in women who breastfeed compared with those who do not. The first menstrual flow may occur as early as the second month or as late as the 18th month after delivery.
 - (1) Amenorrhea during lactation is due to a lack of appropriate ovarian stimulation by pituitary gonadotropins.
 - (2) Nevertheless, pregnancy can occur with lactation. Nursing mothers must understand that ovulation and pregnancy can occur even in breastfeeding amenorrheic women.
6. **Family planning.** Methods of contraception should be fully reviewed and implemented (see Chapter 24).
 - a. **Nonlactating mothers** may begin using a contraceptive soon after delivery if they wish to avoid becoming pregnant. Combination of oral contraceptives, depo-medroxyprogesterone acetate, or subdermal etonogestrel implant may be offered before discharge.
 - b. **Lactating mothers** may begin using progestin-only oral contraceptives as soon as their milk supply is established. **Progestone-only contraceptives** such as oral contraceptive pills, depo-medroxyprogesterone acetate, etonogestrel subdermal implant, do not appear to have adverse effects on lactation. Combined oral contraceptives (containing estrogen and progestins) should not be used.
 - (1) Intrauterine devices (IUDs) do not interfere with breast milk. However, IUDs are generally not inserted until 4 to 6 weeks' postpartum.
 - (2) Diaphragms or cervical caps cannot be fitted adequately during the immediate postpartum period, and their use should be delayed until after the 4- to 6-week examination.
 - (3) Spermicides and barrier methods have no effect on breastfeeding. Lubricated condoms may offset vaginal dryness secondary to breastfeeding.
 - c. Patients for whom the use of oral contraceptives is contraindicated or who prefer other methods of contraception, such as foam or condoms, should also be offered instructions in their use. Fertility awareness methods, such as the rhythm method, are difficult to practice accurately before the resumption of menses and therefore are not recommended.

B Complications The most common complications include hemorrhage, genital tract infections, urinary tract infections, and mastitis.

1. **Postpartum hemorrhage** is defined as a blood loss in excess of 500 mL during the first 24 hours after vaginal delivery.
 - a. **Causes**
 - (1) **Failure of compression of blood vessels at the implantation site** of the placenta because of:
 - (a) An **atonic uterus** due to general anesthesia; overdistension of the uterus from a large fetus, hydramnios (excess amniotic fluid), or multiple fetuses; prolonged labor; very rapid labor; high parity; or a labor vigorously stimulated with oxytocin. **The most common cause of postpartum hemorrhage is uterine atony.**
 - (b) **Retention of placental tissue**, as seen in placenta accreta, a succenturiate placental lobe, or a fragmented placenta.
 - (2) **Trauma to the genital tract** because of:
 - (a) Episiotomy
 - (b) Lacerations of the cervix, vagina, or perineum
 - (c) Rupture of the uterus

- (3) **Coagulation defects**, either congenital or acquired, as seen in hypofibrinogenemia or thrombocytopenia
 - b. **Management should be directed at the underlying cause(s)**
 - (1) **Vigorous massage** of the uterine fundus for uterine atony
 - (2) **Use of uterine contraction agents** for uterine atony
 - (a) **Oxytocin** 20 U in 1,000 mL of lactated Ringer's solution intravenously.
 - (b) **Methylergonovine** 0.2 mg intramuscularly or intravenously. Because methylergonovine may cause hypertension, it should be avoided in patients with preeclampsia.
 - (c) **Prostaglandin F_{2α}** 0.25 mg intramuscularly up to eight doses at 20-minute intervals. Contraindications include severe asthma.
 - (3) **Manual exploration** of the uterine cavity for retained placental fragments or uterine rupture
 - (4) **Inspection** of the cervix and vagina for lacerations
 - (5) **Curettage** of the uterine cavity
 - (6) Hypogastric artery **ligation; embolization** of the uterine vessels; and, rarely, **hysterectomy**
2. **Puerperal infection** is defined as any infection of the genitourinary tract during the puerperium accompanied by a temperature of **100.4°F (38°C) or higher** that occurs for at least two of the first 10 days postpartum, **exclusive of the first 24 hours**. Prolonged rupture of the membranes accompanied by multiple vaginal examinations during labor is a major predisposing cause of puerperal infection.
- a. **Pelvic infections**
 - (1) **Endometritis (childbed fever)**, the most common form of puerperal infection, involves primarily the endometrium and the adjacent myometrium. The frequency of endometritis is lower in women having vaginal delivery (1% to 3%) than in women having cesarean section without labor and rupture of membrane (5% to 15%). When cesarean section is performed after the onset of labor and ruptured membrane, the frequency of infection is increased from 30% to 35% without antibiotic prophylaxis and 15% to 20% with prophylaxis.
 - (2) **Parametritis**, infection of the retroperitoneal fibroareolar pelvic connective tissue, may occur by:
 - (a) Lymphatic transmission of organisms
 - (b) Cervical lacerations that extend into the connective tissue
 - (c) Extension of pelvic thrombophlebitis
 - (3) **Thrombophlebitis** results from an extension of puerperal infection along pelvic veins.
 - b. **Urinary tract infections** are common during the puerperium because of:
 - (1) **Trauma** to the bladder from a normal vaginal delivery
 - (2) A **hypotonic bladder** from conduction anesthesia
 - (3) **Catheterization**
 - c. **Management.** Precise identification of bacteria specifically responsible for any puerperal infection can be difficult. Historically, genital tract cultures were obtained; however, they are now of little clinical utility because many of the same pathogens were also found in the uterine cavity in clinically healthy puerperal women. Blood and urine cultures may be useful to identify some of these pathogens, especially in women who have undergone cesarean section.
 - (1) **Antibiotics** should be administered according to the sensitivity of the infecting organism to the drug. Broad-spectrum antibiotics, which include anaerobic coverage, are recommended for those pelvic infections in which identification of the offending organism is impossible. **Common organisms include:**
 - (a) **Aerobic** (group B streptococcus, *Enterococcus*, and *Escherichia coli*)
 - (b) **Anaerobic** (*Peptococcus*, *Peptostreptococcus*, *Bacteroides*, and *Clostridium*)
 - (2) **Heparin** should be administered when thrombophlebitis is suspected and a spiking temperature does not respond to intravenous antibiotics. While clinical response should be evidenced in 2 to 3 days after initiation of heparin, the therapy should be continued for 7 to 10 days. The long-term oral anticoagulation is usually not necessary unless other complications such as a pulmonary embolism is present. Broad-spectrum antibiotics should be continued throughout the period of heparin administration.

V

LACTATION

A Physiology Progesterone, estrogen, placental lactogen, prolactin, cortisol, and insulin act together in stimulating the growth and development of the breast's milk-secreting apparatus.

1. **Prolactin**, which is released from the anterior pituitary gland, **stimulates milk production**.
 - a. **Initiation of lactation.** The delivery of the placenta causes a sharp decrease in the levels of estrogens and progesterone, which, in turn, leads to the release of prolactin and the consequent stimulation of milk production.
 - b. **Continued prolactin production.** A stimulus from the breast (e.g., a suckling infant) curtails the release of prolactin-inhibiting factor from the hypothalamus, thus inducing a transiently increased secretion of prolactin.
2. **Oxytocin** is responsible for the **let-down reflex** and the subsequent release of breast milk. Stimulation of the nipples during nursing causes oxytocin to be released from the posterior pituitary gland.

B Nursing Breast milk is ideal for the newborn because it provides a balanced diet. It contains protective maternal antibodies, and the maternal lymphocytes in breast milk may be important to the infant's immunologic processes. Most drugs given to the mother are secreted in low concentrations in the breast milk. Water-soluble drugs are excreted in high concentrations into colostrum, whereas lipid-soluble drugs are excreted in high concentrations into breast milk.

C Mastitis This parenchymatous inflammation of the mammary glands seldom appears before the end of the first week postpartum and not until the third or fourth week postpartum.

1. **Symptoms.** Engorgement of the breasts is accompanied by a temperature increase, chills, and a hard, red tender area on the breast.
2. **Etiology.** The most common offending organism is *Staphylococcus aureus* from the infant's nose and throat, which usually enters the breast through the nipple at the site of a fissure or abrasion during nursing.
3. **Therapy**
 - a. **Gram-positive antibiotic coverage** (e.g., dicloxacillin) is recommended; erythromycin is recommended for penicillin-allergic patients.
 - b. **Heat** should be applied to the breast.
 - c. **Nursing** from the affected breast should continue to decrease engorgement.
 - d. **The abscess should be drained** if the mastitis has progressed to suppuration.
4. **Prevention.** The use of an emollient cream is recommended to help prevent cracking of the nipple.



Study Questions for Chapter 3

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A 41-year-old woman presented to the office with 4-month history of irregular menstrual periods. Her last episode of vaginal bleeding was 3 weeks ago, but only spotted for a day when her normal period usually lasts about 5 days. She reports fatigue with some nausea but without vomiting. She denies any pelvic pain but admits to mild cramping in the lower abdomen at times. She denies any history of sexually transmitted infection nor abnormal Pap smear. You did an office urine pregnancy test which was positive. Your next best step of action after performing a pelvic examination on the patient should be:

- ☐ A Order a CT scan of the pelvis
- ☐ B Order a pelvic ultrasound of the pelvis
- ☐ C Order serum β -hCG quant
- ☐ D Order serum thyroid-stimulating hormone
- ☐ E Do nothing and send the patient home on prenatal vitamins

2. A 26-year-old primigravida woman presented to the office for her first prenatal care visit. The first day of her last menstrual period was September 10, 2010, and the last day was September 15, 2010. She reports regular menstrual cycles every 35 days. She also recalls a positive home urine pregnancy test end of May, and has had no vaginal bleeding since. She denies use of birth control pills, Depo-Provera, or other contraceptive in the last 7 months. What is the best estimate of her due date on the basis of her menstrual history?

- ☐ A June 3, 2011
- ☐ B June 17, 2011
- ☐ C June 24, 2011
- ☐ D December 17, 2011
- ☐ E December 24, 2011

3. During a routine prenatal visit in the office, you noticed that the fundal height of a 23-year-old primigravida woman who is at 32 weeks' gestational age with normal blood pressure is measuring only 28 cm. She has been compliant with her prenatal care since 7 weeks' gestation, and reported a normal appetite. She denies any leakage of fluid per vagina. What is the next best course of action?

- ☐ A Perform a Leopold maneuver and inform patient that the fetus is in breech presentation
- ☐ B Perform an amniocentesis to determine the status of the fetal lung maturity
- ☐ C Repeat prenatal labs, including a 1-hour glucose tolerance test
- ☐ D Perform an ultrasound to determine the estimated fetal weight and amniotic fluid index volume
- ☐ E Perform a cervical examination and send the patient home with instruction to return for routine follow-up

4. A 19-year-old gravida 2, para 1, presents at 39 weeks' gestational age to the labor and delivery unit with complaints of leakage of brown tinged fluid per vagina for 12 hours. She denies contraction, vaginal bleeding, fever, and chills. Her examination revealed positive signs and symptoms of rupture of amniotic fluid. She is afebrile and the fetus is confirmed to be in vertex presentation by ultrasound. Which of the following course of action is indicated?

- ☐ A Induction of labor
- ☐ B Amniocentesis to confirm fetal lung maturity status
- ☐ C Tocolysis with magnesium sulfate
- ☐ D Cesarean section
- ☐ E Administration of glucocorticoids

5. A 25-year-old gravida 5, para 4, woman rapidly delivered an infant weighing 3,900 g upon presenting to the labor and delivery unit without any anesthetic. After an hour, the placenta was manually extracted. A total of 20 U of oxytocin in 1,000 mL of lactated Ringer's solution was initiated intravenously. After

careful inspection of the genital tract, no laceration was noted on the vaginal wall and the cervix. You are called back to the room 30 minutes later by the nurse to evaluate increase vaginal bleeding from the patient. You begin massaging the uterine fundus but her bleeding continues to be brisk. Her fundus appears to be firm, after you have given her a dose of 0.25 m IM Prostaglandin $F_{2\alpha}$. Her blood pressure = 164/92, P = 102, T = 98.9, R = 18. The patient continues to experience intermittent vaginal bleeding. Her total blood loss is estimated at 1,500cc. Which of the following is the best step in management?

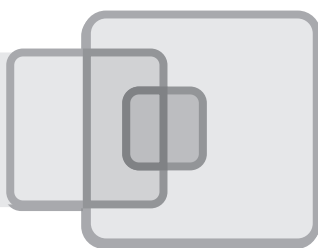
- ☐ A Methylergonovine 0.2 mg intramuscularly
- ☐ B Hypogastric artery ligation
- ☐ C Embolization
- ☐ D Hysterectomy
- ☐ E Manual exploration followed by curettage of the uterine cavity



Answers and Explanations

1. **The answer is C** [IA, IB, IC]. Serum bHCG (quantified) levels may allow one to estimate the stages in a woman's pregnancy during the first trimester. Generally, as the bHCG quant reaches a discriminatory level, a pelvic ultrasound would be able to confirm the viability of an intrauterine pregnancy. This is especially important in women with unsure LMP or history of irregular periods. The one day history of vaginal spotting in this woman may likely not be her normal period, so obtaining a serum bHCG quant will be useful in determining the stage of her pregnancy prior to performing a pelvic ultrasound. A CT scan of the pelvis is contraindicated in a woman with positive HCG due to the exposure to radiation. Obtaining thyroid-stimulating hormone is not useful in this case, as her bHCG levels may interfere and falsely suppress TSH production in the first trimester. Because first trimester bleeding must be worked up until intrauterine pregnancy is confirmed, sending this patient home without confirming her pregnancy stage and status is inappropriate.
2. **The answer is C** [ID]. The calculated due date of 9 months plus 7 days from the last menstrual period is based on the assumption that a woman has 28-day cycles and that ovulation occurs on Day 14 (thus no recent contraception that may change pattern of ovulation). Using Naegele's rule, count back 3 months (September minus 3 months = June) and add 7 days to the first day (not the last day) of the last menstrual period ($10 + 7 = 17$). So far, you have June 17. However, this date is based on a 28-day cycle. Because this patient has 35-day cycles and because the luteal phase of the menstrual cycle is always constant (14 days), ovulation occurred on Day 21 rather than Day 14 (7 days later than you predicted). Therefore, her due date is June 24.
3. **The answer is D** [IB1, IIIA1]. Fundal height measurement is a screening tool used to assess the growth of the fetus during a woman's pregnancy. When the measurement is off (discrepancy between fundal height by 2 cm or more and the gestational age), the obstetrician must follow up by obtaining diagnostic studies to reassure the size of the fetus, the amniotic fluid volume are appropriate. An ultrasound will be able to provide such information with minimal risks. Performing a Leopold maneuver is useful to determine fetal lie but is irrelevant in predicting the growth of the fetus. An amniocentesis has no role in assessing the fetal size and the amniotic fluid volume. It is performed to obtain amniotic fluid to be analyzed for genetic disease or fetal lung maturity status. While a woman with abnormal glucose tolerance may be more likely to develop increase amniotic fluid volume (polyhydramnios), repeating prenatal labs and a one-hour glucose tolerance test now will not be helpful in confirming that the fundal height measurement is lagging. Sending a patient home without further work up for size less than dates would not be appropriate.
4. **The answer is A** [IIC4]. At term, induction of labor is indicated if there is no labor within 6 to 24 hours of rupture of membrane. Fetal lung maturity status is no longer necessary in a term patient as the risk of RDS is minimal. There is also no role of magnesium sulfate and glucocorticoids as the risks of infection after rupture of membrane outweighs the risks of prematurity after 34 weeks' gestation. A cesarean section is not necessary given the fetus is in vertex presentation.
5. **The answer is E** [IVB1b]. While uterine atony is the most common cause of immediate postpartum hemorrhage, retained placental fragment must be considered in delayed postpartum bleeding. Vigorous fundal massage and uterotonic agents may be used to control the immediate bleeding due to atony. Methylergonovine is contraindicated because this patient is hypertensive despite brisk blood loss. If the patient continues to bleed and the uterus is unable to stay contracted and firm, then exploration of the uterine cavity for retain placental tissue, such as placenta accrete, succenturiate lobe may be achieved with aid of an ultrasound machine. Curettage of the uterine cavity will be the necessary next step. If the bleeding continues after curettage, then uterine artery embolization or other surgical interventions such as hypogastric artery ligation and hysterectomy must be considered.

chapter 4



Antepartum Care

DANIELLE BURKLAND

I

INTRODUCTION

Prenatal care begins with preconceptional counseling when a woman is contemplating pregnancy and continues with a comprehensive medical and psychosocial evaluation throughout the antepartum period. The goal of comprehensive prenatal care is to maintain maternal health and deliver a healthy baby while minimizing poor obstetrical and fetal outcomes.

II

PRECONCEPTION CARE

A Annual gynecological visits should include the evaluation of a woman's interest in starting a family. If planning to conceive, the following should be considered:

1. Health history of the mother and the father needs to be assessed. Medical problems that could affect the health of the mother or the fetus during pregnancy should be addressed. Medications should be reviewed and those contraindicated in pregnancy should be stopped. For those with significant medical issues (i.e., significant cardiac disease, diabetes, seizure disorder, hypertension, etc.), referral to a maternal fetal medicine specialist for preconceptional counseling should be considered.
2. Weight
 - a. If obese (body mass index [BMI] greater than 30), patient should be counseled to lose weight prior to conception to improve obstetrical outcomes.
 - b. If underweight (BMI less than 20), patient should be counseled to gain weight prior to conception to improve obstetrical outcomes.
3. Folic acid (0.4 mg) supplementation to reduce the incidence of neural tube defects.
4. Rubella immune status: immunize if nonimmune and advise waiting for 1 month before conception.
5. Varicella immune status: if patient does not recall having the chicken pox; immunize if not immune.
6. Offer cystic fibrosis carrier screening.
7. Depending upon the ethnic background, the following tests may be ordered to screen for genetic diseases:
 - a. Tay-Sachs, Canavan, Niemann-Pick, Fanconi anemia, Bloom syndrome, Gaucher, and familial dysautonomia: Ashkenazi Jews
 - b. Sickle hemoglobinopathies: African Americans
 - c. β -Thalassemias: Mediterranean, Southeast Asians, and African Americans
 - d. α -Thalassemias: Southeast Asians, Mediterraneans, and African Americans
 - e. Tay-Sachs: Ashkenazi Jews, French Canadians, and Cajuns
 - f. If family history is significant for other inherited diseases, genetic counseling for screening for diseases such as fragile X and Duchenne muscular dystrophy may be offered (Table 4–1)

TABLE 4–1 Summary of Antepartum and Peripartum Tests

Test	First Visit	16–20 Weeks	20–24 Weeks	24–28 Weeks	28–32 Weeks	35–37 Weeks
Pap smear	X					
CBC	X				X	
Urine analysis and culture	X					
Type and screen	X			X		
Rh-negative patients				X		
Rubella	X					
Syphilis	X				X*	
HIV	X					
Hepatitis	X					
Gonorrhea and chlamydia	X				X*	
Hemoglobin electrophoresis [†]	X					
PPD	X					
Triple marker		X				
Amniocentesis [‡]		X				
Ultrasound		X				
1-hour glucose tolerance test	X*			X		
Rhogam, if antibody negative					X	
Group β -streptococcus screen						X
Fetal kick count						X

*As indicated or in high-risk populations.

[†]Offered to African American patients, must consider in Asians.

[‡]Offered to women older than 35 years at delivery and patients with increased risk of chromosomal defects on triple marker.

III

CALCULATION OF THE ESTIMATED DATE OF CONFINEMENT

- A** Mean duration of pregnancy is 280 days or 40 weeks.
1. Calculation of the estimated date of confinement (EDC) is most accurate when a woman has regular menses.
 2. It is important to recognize that the first half of the menstrual cycle (follicular phase) is *variable* in length, while the secretory or luteal phase is always for 12 to 16 days.
 3. Calculating the EDC assumes that a woman's menstrual cycle is approximately 28 days with ovulation occurring on Day 14. However, if her cycle is 35 days, then she probably ovulates on cycle Day 21. This would change her EDC.
 4. Accurate dating of pregnancy is essential as clinical decisions are based upon the specific gestational age.
- B Naegele's rule** The EDC is determined by subtracting 3 months and adding 7 days to the first day of the last menstrual period (LMP). For example, if the LMP is July 15, then the EDC is April 22. This assumes a 28-day menstrual cycle with ovulation occurring on Day 14.
- C Ultrasound** may be used to confirm or identify an EDC when the LMP is uncertain.
1. Transvaginal ultrasound allows for early identification of an embryo and the accurate dating of pregnancy by measurement of the crown–rump length.
 2. In general, in the first trimester, if the EDC by LMP differs by more than 6 days based on ultrasound, then the EDC should be adjusted on the basis of ultrasound dating.

3. Subsequently in the second trimester, if the EDC by LMP differs by more than 10 days based on ultrasound, then the EDC should be adjusted on the basis of ultrasound dating.
4. Finally in the third trimester, there is more variation in the size of fetus, so the EDC should be adjusted only by ultrasound if the EDC varies by more than 14 days and there is no earlier ultrasound confirming the EDC.

IV

INITIAL PRENATAL VISIT: HISTORY

A Complete obstetrical history

1. Definitions:
 - a. *Gravida*: describes the number of pregnancies
 - b. *Nulligravida*: describes a woman who is not now and never has been pregnant
 - c. *Parity*: describes a woman who has delivered a fetus
 - d. *Nulliparous*: describes a woman who has never delivered a fetus
 - e. *Primipara*: describes a woman who has delivered only once
 - f. *Multipara*: describes a woman who has delivered more than once
2. Standard nomenclature of prior pregnancies:
 - a. G_P____
 - b. G_: total number of pregnancies including the current pregnancy
 - c. P____(TPAL notation):
 - (1) The first number represents the Total number of full-term deliveries.
 - (2) The second number represents the total number of Preterm deliveries at 20 weeks or greater.
 - (3) The third number represents the total number of spontaneous or therapeutic Abortions as well as ectopic pregnancies occurring before 20 weeks of gestation.
 - (4) The fourth number represents the total number of Living children.

B For each prior pregnancy, the following information should be obtained:

1. Estimated gestational age at the time of delivery
2. Weight of infant
3. Anesthesia
4. Mode of delivery:
 - a. SVD: spontaneous vaginal delivery
 - b. VAVD: vacuum-assisted vaginal delivery
 - c. FAVD: forceps-assisted vaginal delivery
 - d. Cesarean section, including indication and type of uterine incision
 - (1) Low transverse: incision in lower uterine segment in transverse fashion
 - (2) Classical: vertical incision through the muscular portion of the uterus

C Identification of prior pregnancy complications

1. History of cervical insufficiency will require counseling about prophylactic cerclage placement
2. History of prior preterm birth or preterm premature rupture of membranes will require counseling about 17 α -hydroxyprogesterone injections
3. History of gestational diabetes, preeclampsia, and shoulder dystocia

D Complete medical, surgical, and gynecological history

1. Women with medical diseases such as pregestational diabetes and chronic hypertension require additional counseling, laboratory evaluation, and fetal surveillance
2. Medications and any possible exposures in the first trimester

E Thorough family history of both parents

F Social history including screening for substance abuse and domestic violence

1. Substance abuse—including tobacco, alcohol, and other drugs

2. Domestic violence/intimate partner violence
 - a. Trauma from DV/IPV is a frequent cause of maternal death
 - b. Prevalence between 4% and 8%
 - c. Likelihood of disclosure increases with repeated inquiries

V

INITIAL PRENATAL VISIT: PHYSICAL EXAMINATION AND SCREENING

- A** Complete physical examination should be performed at the initial visit.
1. Height, weight, BMI calculation, and blood pressure should be recorded.
 2. A systolic flow murmur may be heard at the left sternal border, which is normal in pregnancy.
 3. Pelvic examination should include evaluation for abnormal vaginal discharge, performance of cervical cultures and Pap smear if indicated, assessment of cervix and uterine size, and assessment of the bony pelvis.
 - a. **Chadwick sign** is a bluish-red hue of the cervix seen in the first trimester.
 - b. **Clinical pelvimetry:** A pelvis with a diagonal conjugate greater than 11.5 cm is considered to be adequate for delivery of a normal-sized fetus (Fig. 4–1).
 - (1) **Diagonal conjugate** is a measure from the sacral promontory to the anterior inferior pubic symphysis, which can be measured on pelvic examination.
 - (2) **Obstetrical conjugate** is the length from the sacral promontory to the posterior pubic symphysis. This measurement is determined by subtracting 1.5 to 2 cm from the diagonal conjugate. *The obstetrical conjugate is the shortest anterior posterior diameter through which the fetal head must pass.*
 - c. **Pelvic types** (Fig. 4–2)
 - (1) **Gynecoid:** most common type (50%), overall shape is round; the posterior sagittal diameter of the inlet is only slightly shorter than the anterior sagittal diameter; ischial spines are not prominent; a wide pubic arch
 - (2) **Android:** seen in about one-third of white women and one-sixth of nonwhite women; overall shape is heart-like; the posterior sagittal diameter of the inlet is much shorter than the anterior sagittal, limiting the posterior space for the fetal head; ischial spines are prominent; a narrow pubic arch
 - (3) **Anthropoid:** seen in about one-fourth of white women and one-half of nonwhite women; overall shape is long and oval; the anteroposterior diameter is greater than the transverse; prominent ischial spines; narrow pubic arch
 - (4) **Platypelloid:** least frequent, seen in less than 3% of women; flattened shape with short anteroposterior diameter and wide transverse diameter

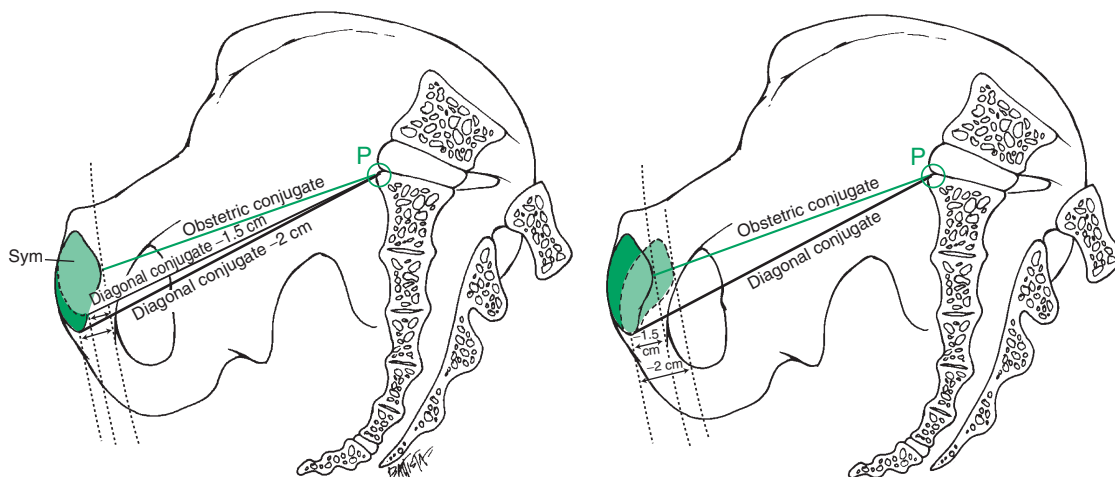


FIGURE 4–1 Variations in length of diagonal conjugate dependent on height and inclination of the symphysis pubis. P, sacral promontory; Sym, pelvic symphysis. (Reprinted with permission from Cunningham FG, MacDonald PC, Gant NF. Williams Obstetrics. 21st Ed. New York: McGraw-Hill, 2001:59, Figure 3–29.)

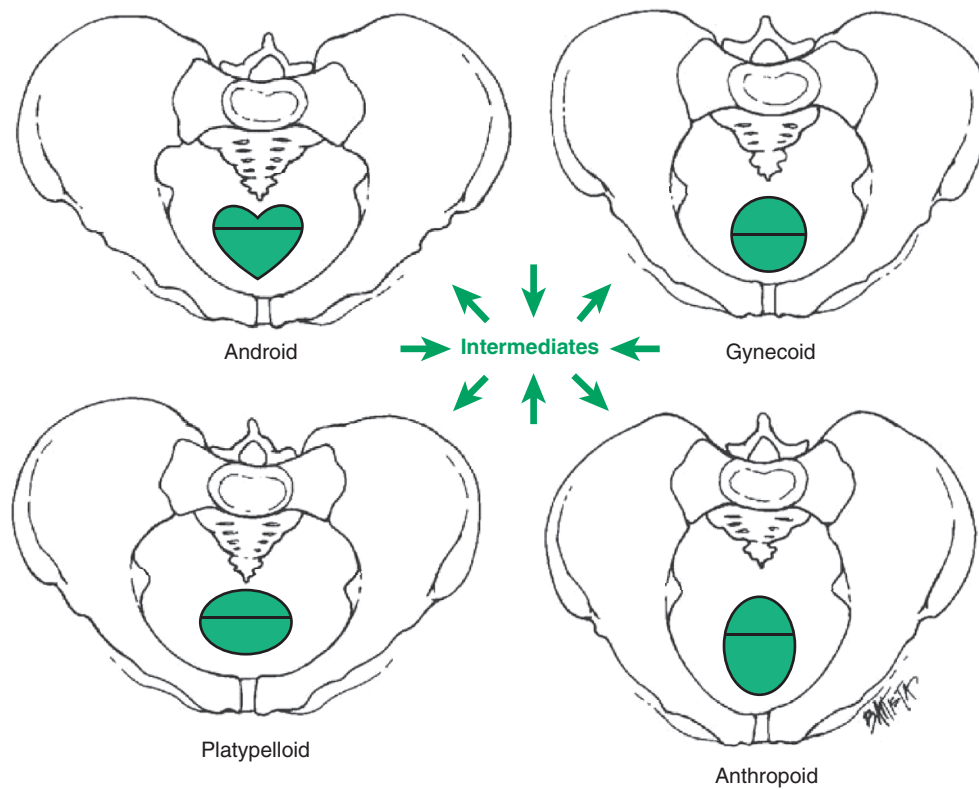


FIGURE 4-2 The four parent pelvic types of the Caldwell-Moloy classification. A line passing through the widest diameter divides the inlet into posterior and anterior segments. (Reprinted with permission from Cunningham FG, MacDonald PC, Gant NF. *Williams Obstetrics*. 21st Ed. New York: McGraw-Hill, 2001:57, Figure 3-27.)

d. Initial prenatal blood work

- (1) Blood type and antibody screen, complete blood count (CBC), rubella immune status, syphilis screen, hepatitis B surface antigen, HIV status, urinalysis, and urine culture
- (2) All patients should be offered cystic fibrosis screening
- (3) Based on the family history and ethnic background may offer specific genetic screening for certain diseases (see II A 7)
- (4) Cervical culture for gonorrhea and chlamydia
- (5) Pap smear, if indicated, based on the age and screening history
- (6) PPD for exposed women or for women from endemic areas
- (7) Early 1-hour glucose tolerance test for women with a history of gestational diabetes or a prior macrosomic infant (more than 4,000 g)

VI

ANEUPLOIDY SCREENING

A General considerations All patients should be offered options for genetic screening and diagnostic testing.

B Screening options have expanded in recent years

1. **First trimester screening (FTS)** is performed between 10 and 13 weeks
 - a. FTS involves measurement of nuchal translucency by ultrasound and two serum analytes: pregnancy-associated plasma protein A (PAPP-A) and free β -human chorionic gonadotropin (β -hCG).
 - b. FTS permits earlier diagnostic testing for positive tests.
 - c. FTS does not screen for neural tube defects.
2. **QUAD screen** is performed in the second trimester, 15 to 20 weeks
 - a. QUAD screen involves four serum analytes: α -fetoprotein (AFP), hCG, unconjugated estriol, and inhibin-A.

- (1) Trisomy 21 is associated with decreased levels of AFP and estriol and increased levels of hCG and inhibin.
- (2) Trisomy 18 is associated with decreased levels of CFP, hCG, and estriol.
- (3) **Integrated and sequential screens.** In this algorithm, a combination of both first trimester and second trimester screens are performed.
 - (a) In **sequential screening**, the result of the first trimester screen is released to the patient and provider.
 - (b) In **integrated screening**, the result of the first trimester test is withheld and incorporated into a final overall risk assessment.

VII

SUBSEQUENT PRENATAL VISITS

A Frequency

1. In Uncomplicated pregnancies, visits occur every 4 weeks until 24 to 28 weeks, and then the frequency increases to every 2 to 3 weeks. After 36 weeks, visits occur every week until delivery.
2. Complicated pregnancies require closer surveillance.

- #### B
- Each visit includes maternal weight, blood pressure, urine dip for glucose and protein, assessment of uterine size, and fetal heart tones.

C Milestones

1. By 20 weeks: complete genetic screening if desired and level II ultrasound for fetal anatomical evaluation.
2. At 26 to 28 weeks: complete 1-hour glucose tolerance test to screen for gestational diabetes and a third-trimester CBC. If patient is Rh-negative, RhoGAM (300 µg) should be administered after a repeat antibody screen. Consider repeat syphilis and HIV screening in high-risk populations.
3. Between 35 and 37 weeks: group B streptococcus swab should be performed. Consider repeat chlamydia screening. Leopold maneuvers should be used to determine fetal presentation and estimated fetal size.
4. After 41 weeks: nonstress test should be performed twice weekly.

- #### D
- Patients should be reminded of concerning signs to look out for throughout the pregnancy.
1. After 20 weeks, preterm labor precautions should be given to patient.
 2. After 28 weeks, patients should be instructed to do fetal kick counts. Normal fetal movement is 10 fetal movements in 2 hours.
 3. After 35 weeks, patients should be given warning signs of preeclampsia and term labor instructions.

VIII

NUTRITION

- #### A
- The recommended weight gain** during pregnancy depends on the prepregnancy weight and health of the woman. Recent institute of medicine (IOM) guidelines are as follows:

1. BMI less than 19: 28 to 40 lb
2. BMI 19 to 25: 25 to 35 lb
3. BMI 25 to 29: 15 to 25 lb
4. BMI greater than 30: 11 to 20 lb

- #### B
- Calories** In general, caloric intake should be 25 to 35 kcal/kg of ideal body weight. An increase of 100 to 300 kcal/d is recommended in pregnancy.

C Dietary composition

1. Protein: requirement is about 1.1 g/kg/d.
 - a. Required for fetal growth.
 - b. Best sources are from animal sources such as meat, milk, eggs, poultry, and cheese.

2. Iron: recommended intake is 30 mg elemental iron per day.
 - a. Even in a well-balanced diet, it is hard to maintain adequate iron stores during pregnancy.
 - b. Most women need supplemental iron, which is found in prenatal vitamins.
 - c. Some women may require still more iron supplementation.
3. Calcium: recommended intake is 1,000 mg daily from diet or with addition of calcium supplement.
4. Folic acid: recommended intake is 400 to 1,000 $\mu\text{g}/\text{d}$ to prevent neural tube defects.
 - a. For women with history of infant with neural tube defect, recommended intake is 4 mg/d.
5. Avoid unpasteurized cheeses, raw shellfish, and fish that have high mercury levels such as shark, tilefish, king mackerel, and swordfish. Limit the fish intake to 12 oz/wk.
6. Avoid excess vitamin A (no more than 4,000 IU/d).

IX

LIFESTYLE MODIFICATIONS

- A Exercise** It is not necessary to limit exercise although the level of intensity should not be increased during pregnancy. Restriction may occur if complications of pregnancy such as preterm labor occur.
- B Travel** Air travel does not have a harmful effect on pregnancy. It is permissible to fly up to 36 weeks. Pregnant women on long flights should be advised to stay hydrated and move around the cabin every 2 hours to reduce the risk of deep vein thrombosis.
- C Coitus** In uncomplicated pregnancies, sexual intercourse does not pose harm to the pregnancy.
- D Substance use and abuse** All pregnant patients should be screened for alcohol, nicotine, and other drug use including recreational use of prescription drugs. Estimation that one in ten neonates is exposed to one or more mood altering drugs in utero.
1. **Smoking** should be strongly discouraged during pregnancy. Smoking has been associated with low-birth-weight infants, preterm rupture of membranes, placental abruption, placenta previa, and sudden infant death syndrome. Elimination of all smoking during pregnancy would decrease the perinatal mortality rate by 5%.
 2. **Alcohol** should be avoided during pregnancy as no known safe threshold is known. Fetal abnormalities include mental retardation and neurodevelopmental deficits. Fetal alcohol syndrome is characterized by craniofacial defects, growth restriction, and CNS dysfunction.
 3. **Other drugs.** The use of other drugs should be screened for. Often women who use cocaine, heroin, and other drugs may not present for routine antenatal care.
- E Caffeine** Caffeine has not been associated with teratogenic effects. Caffeine has been associated only with spontaneous abortion at very high levels (greater than five cups per day).
- F Flu shot** The Centers for Disease Control and Prevention (CDC) recommends all pregnant women to have flu shot; the injectable inactivated and not the intranasal version.
- G Medications** Most drugs administered during pregnancy cross the placenta and reach the fetus. Exceptions are the large organic ions such as heparin and insulin. The Food and Drug Administration (FDA) created five categories on the basis of the risk to the fetus. Package inserts that include FDA classification should be consulted when prescribing medication in pregnancy.
1. **Category A** (e.g., levothyroxine, folic acid). Well-controlled studies in pregnant women show no risk to the fetus in any trimester of pregnancy.
 2. **Category B** (e.g., ondansetron, penicillins). Well-controlled studies in pregnant women have shown no increased risk of fetal abnormalities despite adverse findings in animals. Drugs are also placed in this category if, in the absence of adequate human studies, animal studies show no fetal risk. The chance of fetal harm is remote but possible.

3. **Category C** (e.g., prochlorperazine, trimethoprim-sulfamethoxazole). Well-controlled human studies are lacking, and animal studies are lacking as well or have shown a risk to the fetus. There is a **chance of fetal harm if the drug is administered in pregnancy**. However, the potential benefits may outweigh the potential risk.
4. **Category D** (e.g., phenytoin, carbamazepine). Studies in humans have demonstrated a risk to the fetus; therefore, the **drug should not be administered during pregnancy**. However, the potential benefits may be acceptable in cases of a life-threatening situation or serious disease for which a safer drug cannot be used or has proven ineffective.
5. **Category X** (e.g., diethylstilbestrol, thalidomide, accutane). Studies in animals or human have demonstrated **evidence of fetal abnormalities or risk** that clearly outweigh any possible benefit to the patient.



Study Questions for Chapter 4

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A woman presents to your office for prenatal care. She has had two abortions, one ectopic pregnancy, a fetal demise at 37 weeks' gestation, and three live births. Her son, who is now 13 years old, was delivered at 34 weeks' gestation by spontaneous vaginal delivery. Her daughter, who is now 10 years old, was delivered at 38 weeks' gestation by cesarean section secondary to fetal distress during labor. Her youngest daughter, who is now 5 years old, was delivered at 33 weeks. What are her "Gs and Ps" by simple notation and by TPAL notation, respectively?

- ☐ A G₇ P₃ and G₇ P₂₂₃₃
- ☐ B G₈ P₃ and G₈ P₂₂₃₃
- ☐ C G₇ P₃ and G₇ P₃₁₃₄
- ☐ D G₇ P₃ and G₇ P₂₂₃₄
- ☐ E G₈ P₃ and G₈ P₄₀₃₃

2. A 19-year-old woman, gravida 2, para 1 at 28 weeks' gestation presents to your office for routine prenatal care. She delivered her daughter vaginally at 39 weeks without any complications. Her medical history is unremarkable, and her current pregnancy has been complicated by several missed prenatal visits. Her BP is 108/73; her temperature is 96.8°F, her fundus measures at 28 weeks, she is 5 feet 4 inches tall, her prepregnancy weight was 120 lb, and she now weighs 135 lb. She is rubella nonimmune, hepatitis B surface antigen-negative, O +/antibody, RPR nonreactive, and gonorrhea culture/chlamydia negative. All of the following would be appropriate except:

- ☐ A Measles Mumps Rubella (MMR) vaccine
- ☐ B 50-g glucose tolerance test
- ☐ C 300-μg anti-D immune globulin if Rh-negative
- ☐ D CBC
- ☐ E Repeat HIV and syphilis screening

3. A 38-year-old African American woman, gravida 1, para 0010 presents for preconception care. Her medical history includes obesity with a BMI of 42, diabetes, and tobacco use. Her obstetrical history is notable for an elective termination at 18 weeks of a fetus with anencephaly. She desires to conceive. Your recommendations would include the following:

- ☐ A Supplement diet with folic acid, 4 mg daily
- ☐ B Start a diet and exercise program to improve obstetrical outcomes
- ☐ C Obtain optimal glycemic control before conception to reduce risk of fetal anomalies
- ☐ D Tobacco cessation program
- ☐ E Tay-Sachs and sickle cell disease screening

4. A Vietnamese couple present for their first prenatal visit. She is a 36-year-old G₁ P₀ at 8 weeks' gestation by LMP with no medical problems. The appropriate initial prenatal assessment includes all of the following except:

- ☐ A CBC
- ☐ B Domestic violence screening
- ☐ C Discussion of aneuploidy screening such as sequential screening
- ☐ D α-Thalassemia screening
- ☐ E Tay-Sachs carrier screening

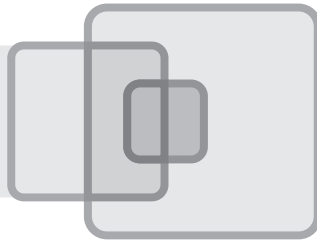
5. An 18-year-old woman, gravida 2, para 1 presents for her first prenatal visit. She reports regular 28 days' cycles and her LMP was September 9. She is 15 weeks 3 days by LMP. She is measuring size greater than dates and you perform an ultrasound that differs by 18 days. What is her EDC calculated by Nagele's rule and would you continue to use that EDC?

- ☐ A June 16 and no
- ☐ B December 16 and no
- ☐ C December 2 and yes
- ☐ D December 16 and yes
- ☐ E June 16 and yes



Answers and Explanations

1. **The answer is B.** In this question's scenario, the woman has been pregnant now eight times (her current pregnancy = 1, two abortions = 2, one ectopic = 1, one term fetal demise = 1, and three live-births = 3; $1 + 2 + 1 + 1 + 3 = 8$). For the **TPAL** notation, **T** refers to the number of term infants delivered regardless of outcome (fetal demise at 37 weeks and term delivery at 38 weeks = 2); **P** stands for preterm (preterm delivery at 34 weeks and 33 weeks = 2); **A** stands for abortions, either elective or miscarriages (also includes ectopic pregnancies) (2 abortions + 1 miscarriage = 3); and **L** refers to the number of living offspring (son and two daughters = 3). With multiple gestation pregnancies, the parity does not increase by the number of babies delivered (e.g., a patient who has been pregnant once and delivered twins at 38 weeks would be noted as G₁ P₁ and G₁ P₁₀₀₂).
2. **The answer is A.** MMR vaccine is a live-attenuated vaccine and should not be given during pregnancy. At 28 weeks, it is routine to perform a glucose tolerance test and repeat CBC. In patients who are RH-negative, a repeat antibody screen should be performed and RhoGAM given. In patients with increased risk, repeat HIV and syphilis screening is recommended. This patient might be at greater risk given the poor compliance with prenatal visits.
3. **The answer is E.** The patient has a history of a fetus with anencephaly. Patients with history of neural tube defect (NTD) should increase folic acid to 4 mg/d. Also, optimal glycemic control with a hemoglobin A1C less than 6 will reduce fetal malformations. The patient is obese and thus would benefit from a nutrition and exercise counseling. Tobacco use is associated with several adverse obstetrical outcomes and cessation program prior to conception would also be beneficial. Although sickle cell carrier status is prudent in an African American patient, Tay-Sachs screening is not necessary in this patient.
4. **The answer is E.** All initial prenatal visits and assessments should include domestic violence screening and CBC. The couple are from Vietnam and are at risk for α -thalassemia, so this screening should be done. All patients should be offered genetic screening for aneuploidy. Tay-Sachs is a genetic disease that is prevalent in Ashkenazi Jews, French Canadians, and Cajuns, and therefore does not need to be offered to this couple.
5. **The answer is A.** Nagele's rule tells us to subtract 3 months and add 7 days to LMP in order to calculate an EDC. The correct EDC would be June 16. Since an ultrasound was performed in the second trimester that differs by more than 10 days (18 days in this case), the EDC should be recalculated on the basis of that ultrasound.



Identification of the High-Risk Pregnant Patient

JACK LUDMIR • DOMINIC MARCHIANO

I

INTRODUCTION

For the majority of women, pregnancy and childbirth is a normal physiologic process that results in the delivery of a healthy infant; however, certain circumstances may place a mother or an infant at risk for morbidity. A pregnancy is defined as **high risk** when the likelihood of an adverse outcome is greater than in the general pregnant population. A program of routine prenatal care may optimize pregnancy outcome by achieving the following goals:

- A** Providing **advice, reassurance, education, and support** for the woman and her family
- B** Managing the **minor ailments** of pregnancy
- C** Providing a **screening** program to confirm that a woman continues to be at low risk
- D** **Preventing, detecting, and managing** factors that adversely affect the health of the mother and the infant

II

MATERNAL AND PERINATAL MORTALITY

A Definitions

1. **Maternal death** occurs either during pregnancy or within 42 days of the termination of pregnancy.
2. The **maternal mortality ratio** is the number of maternal deaths per 100,000 live births. Maternal mortality in the United States has decreased substantially in the past few decades—from 582 per 100,000 live births in 1935 to 12.7 per 100,000 live births in 2004. The maternal mortality rate for blacks has also declined, but it remains higher than for white women (26.5 vs. 10.0 per 100,000 live births); this disparity has widened since 2000. According to the National Center for Health Statistics, the risk of maternal death increases for women older than 30 years, regardless of race. Women aged 35 to 39 years have more than three times the risk of maternal death as women aged 20 to 24 years. Major causes of maternal death in nonabortive pregnancies (excluding ectopic pregnancies) are, in descending order, **hypertensive disorders of pregnancy, obstetric hemorrhage, and thromboembolism**.
3. **Perinatal mortality** is the combination of fetal deaths (after 20 weeks' gestation or weighing more than 500 g) and neonatal deaths (up to 28 days after birth) per 1,000 live births. The perinatal mortality rate has fallen drastically in the last 30 years, from about 29 per 1,000 in 1970 to less than 10.7 per 1,000 in 2004. Of these, 6.2% occur in the fetal stage and 4.5% occur in the neonatal period. Blacks have double the rate of perinatal mortality compared to whites (20.3 vs. 9.1 per 1,000 live births). The factors responsible for this significant discrepancy remain unclear. In general, women without prenatal care have higher rates of perinatal mortality.

III

PRECONCEPTION CARE

- A** Preconception care involves identifying those conditions that could affect a future pregnancy but may be ameliorated by early intervention, such as hypertension, diabetes mellitus, or other metabolic and inherited disorders.
- B** Women (and their partners) who are contemplating pregnancy should be evaluated for conditions that may affect a future pregnancy. Reproductive, family, genetic, and medical histories should be reviewed (see below).

IV

INITIAL PRENATAL VISIT

A General history

1. **Socioeconomic status.** Low socioeconomic status increases the risk of perinatal morbidity and mortality.
2. **Age** is an identifiable risk factor.
 - a. **Maternal age younger than 20 years of age** increases the risk of the following conditions:
 - (1) Premature births
 - (2) Late prenatal care
 - (3) Low birth weight
 - (4) Uterine dysfunction
 - (5) Fetal deaths
 - (6) Neonatal deaths
 - b. **Maternal age older than 35 years of age** increases the risk of the following conditions:
 - (1) **First-trimester miscarriage.** The miscarriage rate for women older than 40 years is three times higher than for women younger than 30 years.
 - (2) **Genetically abnormal concepti.** The risk for fetal chromosomal anomalies increases in direct proportion to maternal age. (This increase may also explain, in part, the increase in first-trimester miscarriages.) **Trisomy 21** represents 90% of the chromosomal abnormalities, but the incidence of other autosomal trisomies (i.e., 13 and 18) and sex chromosomal anomalies also increases with the advancing age.
 - (3) **Medical complications**
 - (a) Hypertension
 - (b) Diabetes
 - (c) Preeclampsia—the incidence of preeclampsia increases with age; it is 6% at 25 years of age, 9% at 35 years of age, and 15% at 40 years of age
 - (4) **Multiple gestation.** The incidence of multiple gestation increases with age. The rate of dizygotic twins is 3 per 1,000 live births in women younger than 21 years of age, and it increases to 14 per 1,000 live births in women 35 to 40 years of age.
 - (5) **Higher rate of cesarean section.** Part of the increase may be attributed to a greater incidence of placenta previa, abnormal presentations, multiple gestation, and medical complications.
 - (6) **Fetal morbidity and mortality.** Women older than 40 years of age have higher rates of stillbirth and low birth weight compared with younger women.
3. **Substance abuse** (see Chapter 8)
 - a. **Tobacco.** A dose–response relationship exists between heavy cigarette smoking and increased fetal morbidity and mortality.
 - b. **Drugs.** The maternal and fetal consequences of drug addiction in pregnancy depend on the drug ingested. Many (e.g., cocaine, opioids, or marijuana) are associated with low birth weight, and drugs such as cocaine and opioids are associated with neonatal withdrawal. Cocaine is also associated with premature labor, abruptio placentae, fetal demise, and maternal complications such as stroke, seizures, cardiomyopathy, and myocardial infarction.
 - c. **Alcohol.** Fifteen percent of pregnant women drink alcohol and 2% drink at least seven drinks per week. Not only does alcohol abuse undermine maternal health, but also a pattern of

TABLE 5–1 Alcohol Abuse Screening: The T-ACE Questionnaire

T: Tolerance; how many drinks does it take to make you feel “high”? Or how many drinks can you hold? (A positive response is two or more drinks.)

A: Have people annoyed you by criticizing your drinking?

C: Have you ever felt you ought to cut down on your drinking?

E: Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (*eye-opener*)?

Scoring: The tolerance question carries substantially more weight (two points) than the three other questions (one point each).

These questions were found to be significant identifiers of risk of drinking in pregnancy (i.e., alcohol intake potentially sufficient to damage the embryo/fetus).

From Sokol RJ, Martier SS, Ager JW. The T-ACE questions: practical prenatal detection of risk-drinking. *Am J Obstet Gynecol* 1989;160:863.

abnormalities known as the **fetal alcohol syndrome** manifests in varying degrees of severity in the fetus (facial anomalies, low-set ears, microphthalmia, congenital heart malformations, micrognathia, microcephaly, and mental retardation), complicating 1 in 1,000 live births. Regular screening for alcohol abuse should be carried out using tools such as the T-ACE questionnaire (Table 5–1).

- d. **Caffeine.** Caffeine-containing beverages, including coffee, are frequently consumed by pregnant women. There is no increased risk of congenital anomalies; however, a recent study suggested higher rates of spontaneous abortion with caffeine intake.

4. Environmental risks

- a. **Noxious chemicals** may cause unpleasant symptoms in the mother (i.e., headache, nausea, and lightheadedness). There is no evidence of increased rate for birth defects.
- b. **Radiation and radioactive compounds** have been associated with spontaneous abortion, birth defects, and childhood leukemia.

- 5. **Domestic violence.** Victims of domestic violence are more likely to be abused while pregnant. Such assaults may lead to placental abruption; fetal fractures; rupture of the uterus, spleen, or liver; and preterm labor. It is estimated that 8% of obstetric patients are physically assaulted while pregnant. Questions on personal safety and violence should be addressed during the prenatal period (Table 5–2).

B Obstetric history Previous obstetric and reproductive history is essential to care in subsequent pregnancy.

1. Parity

- a. **Nullipara.** Nulliparous women are at high risk for development of specific problems, including pregnancy-induced hypertension and possible complications caused by relative lack of knowledge of the pregnancy state.
- b. **Multipara.** Grand multiparous women (five or more pregnancies resulting in viable fetuses) appear to be at increased risk for placenta previa, postpartum hemorrhage secondary to uterine atony, and increased incidence of dizygotic twins (which may occur because grand multiparous are usually of advanced age).

- 2. **Ectopic pregnancy.** A woman with a history of ectopic pregnancy has an increased risk of another ectopic pregnancy. It is imperative that she be evaluated by quantitative β -human chorionic gonadotropin (β -hCG) and transvaginal ultrasound once the level is above the discriminatory zone to detect an intrauterine pregnancy (see Chapter 30).

- 3. **Preterm delivery.** The incidence of preterm delivery (delivery before 37 completed weeks' gestation) correlates well with past reproductive performance and increases with each subsequent preterm delivery. The recurrence rate for preterm delivery is as high as 50%. A short cervical length (less than 2.5 cm), as determined by ultrasound at 20 to 24 weeks, has been associated with increased risk of preterm birth. Patients with a history of preterm delivery may benefit from weekly 17-hydroxyprogesterone injections starting in the mid-trimester.

TABLE 5–2 Determination of Frequency and Severity of Physical Abuse during Pregnancy**Abuse Assessment Screen (Circle YES or NO for Each Question)**

1. Have you ever been emotionally or physically abused by your partner or someone important to you?
YES NO
2. Within the last year, have you been hit, slapped, kicked, or otherwise physically hurt by someone?
YES NO

If YES, by whom? (Circle all that apply)

Husband Ex-husband Boyfriend Stranger Other Multiple

Total number of times:

3. Since you've been pregnant, have you been hit, slapped, kicked, or otherwise physically hurt by someone?
YES NO

If YES, by whom? (Circle all that apply)

Husband Ex-husband Boyfriend Stranger Other Multiple

Score each incident according to the following scale:

- 1 = Threats of abuse, including the use of a weapon
 - 2 = Slapping, pushing; no injuries and/or lasting pain
 - 3 = Punching, kicking, bruises, cuts, and/or continuing pain
 - 4 = Beaten up, severe contusions, burns, broken bones
 - 5 = Head, internal, and/or permanent injury
 - 6 = Use of weapon, wound from weapon
- (If any of the descriptions for the higher number apply, use the higher number)

4. Within the last year, has anyone forced you to have sexual activities?

YES NO

If YES, by whom? (Circle all that apply)

Husband Ex-husband Boyfriend Stranger Other Multiple

Total number of times:

5. Are you afraid of your partner or anyone you listed above?

YES NO

From McFarlane J, Parker B, Solken K, et al. Assessing for abuse during pregnancy. *JAMA* 1992;267(23):3176–3178. Copyright 1992, American Medical Association.

4. **Second-trimester pregnancy loss.** Such loss could be the result of an abnormality in the fetus (chromosomal or infectious) or manifestation of a recurrent condition in the mother, such as cervical insufficiency, uterine abnormality, or thrombophilia. Cervical insufficiency is characterized by premature delivery associated with painless cervical dilation. Ultrasound evaluation of the cervix during gestation is an objective way to identify the patient at risk for this condition. These patients may benefit from therapeutic interventions, such as cervical cerclage. Congenital structural uterine abnormalities have also been associated with an increased incidence of reproductive loss. Women with septate or bicornuate uteri have higher rates of preterm delivery than do those with didelphys or unicornuate uteri.
5. **Large infant (more than 4,000 g).** Large size may indicate previously undetected or uncontrolled glucose intolerance and may be associated with subsequent intrapartum complications, such as:
 - a. Difficult vaginal delivery caused by shoulder dystocia
 - b. Cesarean section for arrest of dilation or descent
 - c. Postpartum complications for the neonate, such as hypoglycemia (see Chapter 17 regarding gestational diabetes)
6. **Perinatal death (stillborn or neonatal).** A pregnancy that follows a perinatal death should be observed closely to avoid a similar outcome. Perinatal death may indicate an underlying problem that may or may not have been detected previously, such as:
 - a. Glucose intolerance
 - b. Collagen vascular disease
 - c. Congenital anomalies
 - d. Chromosomal abnormality
 - e. Preterm labor

- f. Hemolytic disease
 - g. Abnormal labor
 - h. Antiphospholipid syndrome (APS)
 - i. Thrombophilia
7. **Cesarean section**
- a. A woman who has had a **previous cesarean section** may attempt a vaginal delivery with a subsequent pregnancy, provided there are no medical or surgical contraindications, such as:
 - (1) **Classical uterine incision.** A trial of labor is contraindicated in patients with a previous incision into the body of the uterus (classical) because of the high risk of uterine rupture (6% to 8%)
 - (2) An **active herpes infection** at term
 - (3) **Myomectomy** with penetration into the endometrium
 - (4) **Placenta previa**
 - b. **Labor in a successive pregnancy** is usually safe in patients with one prior transverse scar. The chance of uterine rupture with labor is less than 1%. Currently, not enough data are available to establish the safety of a trial of labor in women with two or more transverse uterine scars.
 - c. **Women with a history of prior cesarean section** are at greater risk for placental abnormalities such as placenta previa and placenta accreta. They are also at greater risk for hemorrhage and hysterectomy. The risk increases with the number of prior cesarean sections.
8. **Pregnancy-induced hypertension (preeclampsia and eclampsia)**
- a. There appears to be a familial tendency (higher rate for women with affected sisters, mothers, and grandmothers).
 - b. Women with a history of severe preeclampsia early in pregnancy may have an increased risk for development of preeclampsia in subsequent pregnancies.
 - c. Patients with a history of severe preeclampsia should be followed closely in subsequent gestations. Unfortunately, to date, no intervention has been proven to reduce the risk.
9. **History of infertility.** In vitro fertilization (IVF) pregnancies have been associated with a higher risk of preterm deliveries, low birth weight, placenta previa, preeclampsia, and cesarean section. The risk of congenital malformations appears to be similar to spontaneous pregnancies, although uncontrolled studies have suggested a slightly greater risk.

C Medical history

- 1. **Chronic hypertension** (higher than 140/90 mm Hg). Patients with chronic hypertension are at risk of the following conditions:
 - a. Superimposed preeclampsia
 - b. Abruptio placentae
 - c. Perinatal loss
 - d. Maternal mortality
 - e. Myocardial infarction
 - f. Uteroplacental insufficiency
 - g. Cerebrovascular accident
- 2. **Cardiac disease.** Cardiac disorders have both maternal and fetal implications.
 - a. **Heart disease may develop or worsen in pregnant women.** Because of the hemodynamic changes associated with pregnancy, some cardiac lesions are particularly dangerous, such as Eisenmenger syndrome, primary pulmonary hypertension, Marfan syndrome, and hemodynamically significant mitral or aortic stenosis.
 - b. **Fetal growth and development** depend on an adequate supply of well-oxygenated blood. If this supply is limited, as it appears to be with certain cardiac lesions, then the fetus is at risk of abnormal development and even death.
 - c. **Offspring of parents with cardiac disease** have an increased risk of developing cardiac disease in their lifetimes. This is sometimes identified in utero with fetal echocardiography after 20 weeks.
- 3. **Pulmonary disease.** Maternal respiratory function and gas exchange are affected by the associated biochemical and mechanical alterations that occur in a normal pregnancy. The effect of pregnancy on pulmonary disease is often unpredictable. Diseases such as asthma should be

managed as they normally would be. When pulmonary disease affects maternal well-being or compromises the supply of well-oxygenated blood to the fetus, there is need for concern.

4. Renal disease

- a. In a normal pregnancy, the renal system undergoes certain potentially stressful physiologic, anatomic, and functional changes; therefore, **continuous assessment is necessary** in patients with preexisting or developing renal disease.
- b. With proper medical supervision and control of blood pressure, most women with underlying renal disease can have an **uneventful pregnancy** without adverse effects on either the primary disease or the ultimate prognosis, **provided that the woman's creatinine level is below 1.5 mg/100 mL**.
- c. Pregnancy in patients with a history of renal transplant should be followed in conjunction with a nephrologist. About 1 in 50 women of childbearing age with a functioning renal transplant becomes pregnant. More than 90% of pregnancies that continue past the end of the first trimester successfully.

5. Diabetes. The cornerstone of management for women with diabetes is rigid metabolic control to make patients as consistently euglycemic as possible. Ideally, these efforts should begin before conception and continue throughout the pregnancy. The following fetal problems may complicate the pregnancy of a woman with diabetes:

- a. **Congenital anomalies** (two to three times higher than in individuals without diabetes)
- b. **Fetal mortality**
- c. **Neonatal morbidity**, including:
 - (1) Respiratory distress syndrome
 - (2) Macrosomia
 - (3) Hypoglycemia
 - (4) Hyperbilirubinemia
 - (5) Hypocalcemia
 - (6) Polycythemia

6. Thyroid disease. Untreated hypothyroidism or hyperthyroidism may profoundly alter pregnancy outcome. The fetal thyroid is autonomous and is unaffected by maternal thyroid hormone; however, treatment of thyroid disease during pregnancy can be complicated because the fetal thyroid responds to the same pharmacologic agents as does the maternal thyroid.

7. Thromboembolic disease. Pregnancy is associated with increased production of clotting factors by the liver; this places patients at risk for thromboembolic disease. Patients with prior history of thromboembolism or thrombophilia may benefit from prophylactic or therapeutic anticoagulation during gestation and puerperium.

8. Systemic lupus erythematosus. This condition increases the risk of placental abruption, growth restriction, superimposed preeclampsia, and neonatal lupus. The presence of Rho and La antibodies has been associated with greater risk of congenital heart block.

9. Genetic disorders

- a. **Genetic disorders in the mother**, such as phenylketonuria, increase the risk of fetal malformation. Proper maternal diet during conception and pregnancy reduces the risk.
- b. **Historical factors** may help identify the at-risk pregnancy.
 - (1) **Consanguinity.** Marriage between close relatives results in a large pool of identical genes, thereby increasing the possibility of sharing similar mutant genes, resulting in an:
 - (a) Increased risk of miscarriage
 - (b) Increased risk of rare recessive genetic disease in offspring
 - (2) **Ethnicity.** Specific ethnic groups are more prone to specific diseases.
 - (a) **Tay-Sachs disease** (Ashkenazi Jews, French Canadians)
 - (b) **Canavan disease** (Ashkenazi Jews)
 - (c) **Thalassemias** (Mediterranean, Southeast Asian, Indian, or African people)
 - (d) **Sickle cell anemia** (African, Mediterranean, Caribbean, Latin American, or Indian people)
 - (e) **Cystic fibrosis** (Caucasians)

10. **Infectious diseases.** In addition to rubella and syphilis, for which pregnant women are routinely screened, the following infections during pregnancy place the mother and the infant at high risk for potential morbidity and mortality. The **TORCH** syndrome refers to an infection developing in a fetus or newborn caused by **toxoplasmosis**, **rubella**, **cytomegalovirus**, or **herpes simplex**.
 - a. **Cytomegalovirus (CMV)** results in **increased risk of congenital anomalies** with primary infection during gestation and risk of a small-for-gestational-age infant and congenital hearing loss.
 - b. **Herpes simplex virus** may result in **increased risk of neonatal infection** if active viral lesions are present at birth and the infant is born vaginally.
 - c. **Toxoplasmosis** leads to **increased risk of congenital anomalies** in the fetus if infection occurs early in pregnancy.
 - d. **Parvovirus infection** may cause severe anemia in the fetus, resulting in **hydrops** and death.
 - e. **Varicella zoster virus infection** is associated with a **small risk of fetal sequelae**, such as cutaneous scars and limb hypoplasia, if infection occurs early in the pregnancy. The risk of neonatal infection is greater if infection is present within 5 days of delivery.
 - f. **Hepatitis B virus (HBV)** is associated with **no increased risk of congenital anomalies**, but is associated with risk of vertical transmission and neonatal infection (see VI K).
 - g. **HIV** (see VI M)
11. **Autoimmune disorders**, including **APS**, an autoimmune syndrome caused by the lupus anticoagulant and the anticardiolipin antibody. APS may be expressed as one or more of the following:
 - a. Recurrent fetal loss, such as miscarriage or stillbirth
 - b. Placental infarction
 - c. Preeclampsia early in gestation
 - d. Arterial or venous thrombosis, including neurologic disease
 - e. Autoimmune thrombocytopenia
12. **Depression.** Approximately one in ten women will have depression at any point in pregnancy and the postpartum period. Selective serotonin reuptake inhibitors (SSRIs) are commonly used to treat depression, and their use during pregnancy has been well documented. Recently, the use of the SSRI paroxetine (Paxil) has been associated with a greater risk for fetal cardiac malformations. Furthermore, exposure to SSRIs late in pregnancy has been associated with neonatal complications, including jitteriness, weak cry, poor tone, neonatal respiratory distress, and persistent pulmonary hypertension. Because of the great risk of relapse of depression if SSRIs are discontinued, decisions to take them should be individualized, balancing the risks and benefits of taking the medication.

D Medications Various medications have adverse effects on the fetus, and it is imperative that the risks and benefits to the mother and fetus be evaluated and discussed with the patient before starting, continuing, or stopping the use of medications. When counseling patients about such risks and benefits, a baseline malformation rate of 2% to 3% in the general population should always be used (see Chapter 8).

V

PHYSICAL EXAMINATION

Obstetric patients should undergo a thorough physical examination to assess their general health.

- A General examination** Maternal size, which may reflect socioeconomic and nutritional status, has become an important predictive index.
1. A pregnant woman who is **short** or **underweight** is at increased risk for
 - a. Perinatal morbidity and mortality
 - b. Delivering a low-birth-weight infant
 - c. Preterm delivery
 2. **Obesity.** Defined as a body mass index of 30 or greater, obesity presents a medical hazard to the pregnant woman and her fetus. This problem is greater among non-Hispanic black women (49%) compared with Mexican American women (38%) and non-Hispanic white women (31%). Complications that are more likely to develop in an obese woman include:

- a. Hypertension
- b. Diabetes
- c. Fetal macrosomia and shoulder dystocia
- d. Aspiration of gastric contents during the administration of anesthesia
- e. Wound complications
- f. Thromboembolism

B Pelvic examination

1. The **perineum, vulva, vagina, cervix, and adnexa** should be examined and any abnormalities noted that may affect future management (e.g., adnexal masses, cervical lesions, or diethylstilboestrol [DES] cervical stigmata). A Papanicolaou (Pap) smear should be obtained.
2. **Clinical pelvimetry** should be performed to assess adequacy of the maternal pelvis to facilitate vaginal delivery (see Chapter 4).

C Evaluation of the uterus The size of the uterus is evaluated continuously throughout the pregnancy. The estimated date of delivery should be established at the first prenatal visit so that subsequent discrepancies can be evaluated properly. A strong correlation exists between fundal height in centimeters measured from the symphysis pubis and gestational age in weeks beyond 20 weeks. Size greater or lesser than dates should be evaluated by ultrasound to determine accurate pregnancy dating, presence or absence of multiple gestation, fetal growth abnormalities, and/or amniotic fluid disorders. Reproductive tract abnormalities that may be problematic include:

1. **Leiomyomata (fibroids).** The location and the size of the myomas are important in determining possible future sequelae. In general, the pregnancy has an increased risk of being complicated by:
 - a. Abortion
 - b. Premature labor
 - c. Dysfunctional labor
 - d. Postpartum hemorrhage
 - e. Obstruction of labor by cervical or lower uterine segment myomas
 - f. Unstable fetal lie or compound presentation
 - g. Pain caused by degeneration
2. **Cervical insufficiency.** Characterized by premature cervical dilation in the second trimester, with minimal labor contractions. This is most often identified on physical examination, although ultrasound may aid in the diagnosis.
3. **Uterine anomalies** of the bicornuate or septate type may increase the patient's risk of spontaneous miscarriage and adverse pregnancy outcome.

VI

LABORATORY STUDIES

Routine laboratory studies may help to identify a high-risk pregnancy.

A Blood type, including antibody screen

1. **Rh sensitization** may have profound consequences for the fetus and the management of the pregnancy. If maternal sensitization of an Rh-negative woman to red blood cell antigens has occurred (e.g., prior transfusions or prior pregnancies), the resultant antibodies can be transferred to the fetus and cause hemolytic disease in the Rh-positive fetus.
2. The **antibody screen** is also essential for Rh-positive women because other blood group antigens (e.g., Kell, Kidd, or Duffy) can produce severe hemolytic disease in the fetus.

B Syphilis test (venereal disease research laboratory) Syphilis involves several different stages, and the evaluation of each stage is important in assessing fetal risk. Pregnancy complicated by pre-existing or newly acquired syphilis may result in:

1. An uninfected live infant
2. A late abortion (after the fourth month of pregnancy)

3. A stillbirth
4. A congenitally infected infant

C Gonorrhea culture Screening may be either universal or selective, depending on the prevalence of the disease in the patient population. Gonorrhea during pregnancy may be associated with

1. Intrauterine infection, with premature rupture of membranes and preterm delivery
2. Histologic evidence of chorioamnionitis
3. Neonatal eye infection (ophthalmia neonatorum)
4. Clinical diagnosis of sepsis in the neonate
5. Associated maternal arthritis, rash, or peripartum fever

D Chlamydia testing Screening is recommended for all high-risk or symptomatic patients. Infection during pregnancy may result in:

1. Ophthalmia neonatorum
2. Neonatal pneumonia
3. Postpartum endometritis

E Rubella titer

1. The **clinical course** of rubella is no more severe or complicated in the pregnant woman than in the nonpregnant woman of comparable age. However, active maternal infection does carry risk for the fetus, including:
 - a. First-trimester abortion
 - b. Fetal infection, resulting in severe congenital anomalies
2. **Maternal infection in the first trimester** carries with it the greatest risk to the fetus.
3. **Immunization.** If a patient is diagnosed as having a rubella titer of less than 1:8, she should be immunized postpartum.
 - a. The rubella vaccine is not given during pregnancy because it is a live attenuated vaccine.
 - b. There have been no reported cases of congenital rubella from inadvertent administration of the vaccine to pregnant women.

F Complete blood count with red blood cell indices and platelet count

1. **Anemia.** If present, anemia should be evaluated further and treated. **Microcytosis** without anemia may represent a thalassemia and should also be investigated.
2. **Leukocytosis.** A mild leukocytosis is normal in pregnancy; however, a grossly abnormal value needs to be evaluated.

G Urinalysis and culture

1. **Asymptomatic bacteriuria** is prevalent in 3% to 5% of pregnant women. Early detection, treatment, and close follow-up must be instituted.
2. **Acute systemic pyelonephritis.** Asymptomatic bacteriuria predisposes the pregnant woman to the development of acute systemic pyelonephritis, which has serious complications for the mother and fetus and has been associated with premature labor and delivery. Systemic pyelonephritis develops in approximately 20% to 40% of pregnant women with untreated **asymptomatic bacteriuria**.

H Pap smear Baseline cervical cytology should be established. If abnormalities are noted, proper evaluation should be instituted.

I Gestational diabetes screen Screening for this condition should be performed at 24 to 28 weeks' gestation using a 1-hour, 50-g glucose test (see Chapter 17).

J Screening for neural tube defects

1. **Elevated maternal serum α -fetoprotein (MSAFP)** in the second trimester is seen in 80% to 90% of pregnancies in which a fetal **neural tube defect** is present (e.g., anencephaly and spina

bifida). In the presence of an elevated MSAFP, a targeted ultrasound should be performed to rule out:

- a. Incorrect dates (i.e., pregnancy further along than anticipated)
 - b. Multiple gestation
 - c. Fetal demise
 - d. Abruptio placentae
 - e. Other fetal congenital defects (e.g., omphalocele, gastroschisis, and congenital nephrosis)
2. An unexplained elevated MSAFP may be associated with third-trimester complications such as preeclampsia and placental insufficiency.

K Screening for aneuploidy The American College of Obstetricians and Gynecologists (ACOG) has recently recommended that screening for Down syndrome should be offered to all pregnant women regardless of their age. First-trimester screen in the form of ultrasound for nuchal translucency (NT) plus biochemical markers such as pregnancy-associated plasma protein A (PAPP-A) and free β -hCG have a detection rate for Down syndrome of 85%; however, 90% of the second-trimester screen with multiple marker screen (quadruple screen) consists of MSAFP, unconjugated estriol, hCG, and inhibin A. This screen has a detection rate of 81%. Pregnancies affected with Down syndrome usually have a low MSAFP, low estriol, high hCG, and high inhibin A. Individualized counseling should be offered to patients to determine the best screening strategy and the need for further invasive testing in the form of chorionic villi sampling or genetic amniocentesis.

L HBV testing

1. Identification of pregnant women who are positive for HBV surface antigen (HBsAg) is essential because vertical transmission of HBV is an important cause of acute and chronic hepatitis.
 - a. **First-trimester screening programs** should be instituted to identify seropositive women (0.01% to 5% of pregnant patients are seropositive). The neonates of women who test positive can then be treated with passive and active immunoprophylaxis.
 - b. **Groups at high risk** for HBV seropositivity include intravenous drug users, HIV-positive women, and Southeast Asian women.
2. **Universal immunization** of all neonates, even those of HBsAg-negative mothers, has been recommended by the American Academy of Pediatrics. Immunizations should be given at birth, 1 month of age, and 6 months of age.

M HIV testing HIV testing and counseling of all pregnant women are now recommended by the Centers for Disease Control and Prevention (CDC).

1. The rate of **mother-to-infant transmission** has been estimated to be 20% to 30%, regardless of maternal symptoms. Babies can be infected in utero, at the time of delivery, and postpartum via contaminated breast milk.
2. **Zidovudine (AZT)** given to HIV-positive women during pregnancy has been shown to reduce perinatal transmission from 25% to 8.3%.
3. **Elective cesarean section** at 38 weeks' gestation may further reduce the rate of vertical transmission, particularly in patients with higher viral loads.

N Hemoglobin electrophoresis This screen is indicated in all patients at the first prenatal visit. It will help in identifying hemoglobinopathies such as sickle cell disease that can increase the risk for poor obstetrical outcome.

O Group B streptococcus The CDC recommends universal screening of all pregnant patients at 35 weeks' gestation with a vaginal–rectal culture for group B streptococcus (GBS). The patients with positive cultures should receive intrapartum antibiotic prophylaxis with penicillin to reduce the risk of GBS sepsis in the newborn.

VII

RISK ASSESSMENT AND MANAGEMENT OF RISK IN PREGNANCY

Risk is determined on the basis of the patient's history, physical examination, and results of laboratory studies on the first prenatal visit or subsequent visits.

TABLE 5–3 Schematic Risk Factor Management: Past Obstetric History

Risk Factor	Maternal/Fetal Risk	Management
Previous ectopic pregnancy	Recurrence, maternal anxiety	Early ultrasound to confirm intrauterine pregnancy
Previous stillbirth or early neonatal death	Risk depends on cause (not all are recurrent)	Try to establish cause; early review and specific management
Infant weight ≤2 SD	IUGR	Comprehensive fetal ultrasound Ultrasound for weight
>2 SD	Gestational diabetes Another large fetus	Random glucose at 28 and 32 weeks Vigilance in labor
Congenital anomaly	Possible recurrence	Obtain details/diagnosis, possible prenatal diagnosis
Blood antibodies	Hemolytic disease	Specific protocol
Preeclampsia	Recurrence	Assess renal function Obtain comprehensive fetal ultrasound Carefully check blood pressure
Preterm delivery	Recurrence	Specific plan depending on cause
Uterine scar	Uterine rupture, cesarean section	Review of mode of delivery at 36 weeks
Short labor	Recurrence and neonatal problems (e.g., trauma, asphyxia, hypothermia)	Specific management plan at 36 weeks
Postpartum hemorrhage	Recurrence	Specific plan at 36 weeks

IUGR, intrauterine growth retardation; SD, standard deviation above the mean for gestation.

Modified from James D. Organization of prenatal care and identification of risk. In James DK, Steer PJ, Weiner CP, et al., eds. *High Risk Pregnancy Management Options*. Philadelphia: WB Saunders, 1994.

- A** Once an at-risk patient has been identified, a management plan is implemented to prevent adverse outcome; this plan may be empiric or schematic.
- 1. Empiric plan.** The obstetrician decides on the specific management plan on a patient-by-patient basis.
 - 2. Schematic.** The obstetrician implements a specific, predetermined management scheme every time a risk factor is identified. Table 5–3 represents an example of a schematic risk factor management protocol on the basis of the past obstetric history.
- B** To date, no studies compare empiric versus schematic risk factor management with regard to outcome, although a schematic approach is arguably more scientific.



Study Questions for Chapter 5

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A 39-year-old woman, gravida 3, para 3, is contemplating pregnancy. She delivered three healthy boys by vaginal delivery at ages 17, 23, and 27 years, respectively. Her first pregnancy was complicated by low birth weight. Her second pregnancy was unremarkable. She incurred a third-degree laceration after extension of a midline episiotomy upon delivery of her third boy. Her past medical history is unremarkable other than three to four asthma exacerbations every month. Her risk of which of the following is most increased in a subsequent pregnancy, as compared to her prior pregnancies?

- ☐ A Asthma exacerbation
- ☐ B Fourth-degree laceration
- ☐ C Low-birth-weight infant
- ☐ D Twins
- ☐ E Uterine dysfunction

2. A 34-year-old primiparous woman is seeing you because she is considering a second pregnancy. She tells you she is afraid to get pregnant given the outcome of her first pregnancy. At 32 years of age, she delivered a term infant with Down syndrome. During that gestation, a serum screen for aneuploidy was not performed. Had a second-trimester multiple marker screen been performed, which of the following results would have been helpful?

- ☐ A Low MSAFP, low estriol, low hCG, low inhibin A
- ☐ B Low MSAFP, high estriol, low hCG, high inhibin A
- ☐ C Low MSAFP, low estriol, high hCG, high inhibin A
- ☐ D High MSAFP, high estriol, low hCG, low inhibin A
- ☐ E High MSAFP, low estriol, low hCG, low inhibin A

3. A 28-year-old woman, gravida 6, para 1, presents to your office because she tested positive on her home pregnancy test. Her last menstrual period occurred 40 days ago. She normally has regular, 28-day cycles and her periods last 3 to 4 days. She delivered a preterm infant with her very first pregnancy at the age of 17 years. Her subsequent pregnancies have been complicated by three miscarriages and an ectopic pregnancy. She denies any medical problems but admits contracting chlamydia during her late teens (which she sought treatment for). Which of the following is the most important initial step in the management of this patient?

- ☐ A Qualitative serum β -hCG
- ☐ B Quadruple screen (MSAFP, estriol, hCG, inhibin A)
- ☐ C Anticardiolipin antibodies
- ☐ D Chlamydia antibody levels
- ☐ E Obstetric ultrasound

4. A 33-year-old woman, gravida 3, para 2, at 32 weeks' gestation, presents to you for her routine prenatal care. She delivered her first baby by cesarean section due to nonreassuring fetal heart rate pattern on the fetal monitor. Her second baby was also delivered by cesarean section because she did not want a trial of labor. Both infants weighed less than 4,000 g and are doing fine now. You obtain operative records of her cesarean sections, which show a Pfannenstiel skin incision and low classical type of incision of the uterus. Currently, she is interested in vaginal delivery. What is the best advice you can give her?

- ☐ A Vaginal delivery is not recommended because the risk of uterine rupture approaches 8%
- ☐ B Vaginal delivery is recommended because the risk of uterine rupture is less than 1%
- ☐ C Vaginal delivery is not contraindicated with a history of two previous cesarean sections
- ☐ D Vaginal delivery is a possibility, but risk of rupture is between 0.5% and 4%
- ☐ E Vaginal delivery is a possibility, but risk of uterine rupture is 8%

5. A 41-year-old woman, gravida 8, para 4, at 18 weeks' gestation, presents to you for her first prenatal visit. She has a history of three therapeutic abortions as a teenager. She has four healthy children—the first two delivered at 32 weeks' gestation, and her third and fourth children delivered at 35 weeks' gestation. Her past medical history is significant for two episodes of pyelonephritis with her first two pregnancies, as well as a partial bicornuate uterus. What in her history places her at greatest risk for preterm delivery with this pregnancy?

- ☐ A Age
- ☐ B Delivery history
- ☐ C Therapeutic abortions
- ☐ D Pyelonephritis
- ☐ E Uterine anomaly

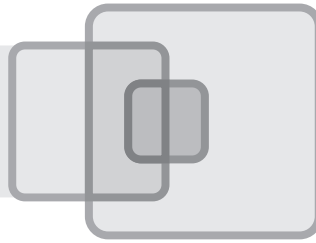
6. A 25-year-old woman, gravida 2, para 1, at 8 weeks' gestation, presents to the high-risk clinic for prenatal care. Her first pregnancy was complicated by delivery of a premature infant with respiratory problems. Her past medical history is remarkable for severe asthma (more than 20 exacerbations per week) for which she uses albuterol and steroid inhalers. She has type II diabetes mellitus that was treated with oral hypoglycemic agents before pregnancy. She also tells you that she acquired hepatitis C a few years ago, when she used to inject intravenous heroin. She is 5 feet 5 inches tall and weighs 120 lb. Her blood pressure is 180/98, and her urine dipstick is negative. Which of the following predisposes her to delivery of an infant with congenital anomalies?

- ☐ A Weight
- ☐ B Liver disease
- ☐ C Diabetes mellitus
- ☐ D Hypertension
- ☐ E Intravenous drug history



Answers and Explanations

1. **The answer is D** [IV A 2 b (4)]. Maternal age older than 35 years is a risk factor for multiple gestation, especially dizygotic. The effect of pregnancy on lung diseases is unpredictable; therefore, you cannot assume that her mild asthma will worsen. A third-degree laceration does not necessarily lead to a fourth-degree laceration in a subsequent pregnancy. Laceration degrees depend on obstetric factors, such as size of the baby and length of a midline episiotomy. Teenage pregnancies are at risk for delivery of low-birth-weight infants and uterine dysfunction.
2. **The answer is C** [VI K]. Trisomy 21 is associated with low MSAFP, low estriol, high hCG, and high inhibin A. It is a screening test that can identify up to 80% of pregnancies with Down syndrome. Multiple marker screens with high MSAFP are associated with neural tube defects.
3. **The answer is E** [IV B 2]. The most important initial step in a patient with a history of an ectopic pregnancy and possible pelvic inflammatory disease history (history of chlamydial infection) who may be pregnant is to perform an obstetric ultrasound to rule out another ectopic pregnancy and to rule in an intrauterine pregnancy. Transabdominal imaging should always be attempted first. If unsuccessful, then transvaginal imaging is indicated. A qualitative serum β -hCG will just confirm that the patient is pregnant. Given that the patient has had a positive home pregnancy test, an in-office, ultrasensitive urine hCG is sufficient to confirm pregnancy. A quantitative serum β -hCG is useful to determine when an intrauterine gestation will be visible on transvaginal ultrasound. In this patient who has regular cycles and is 12 days late, an intrauterine gestation should be visible on transvaginal ultrasound. If not, then serum β -hCG is required. The quadruple screen is not useful when performed before 16 weeks' gestation. Anticardiolipin antibodies may be helpful in the future along with other parameters if the patient is interested in delineating the cause of her recurrent spontaneous abortions. Chlamydia antibody levels are not necessary because you already know that the patient has had a chlamydial infection in the past.
4. **The answer is A** [IV B 7 a (1) and 7 b]. A classical uterine incision (vertical uterine incision through the muscular portion of the uterus) is a contraindication to a trial of labor and vaginal delivery with a subsequent pregnancy. Women with one previous cesarean section are candidates for a vaginal delivery with a subsequent pregnancy, especially if the reason for having the initial cesarean section is nonrepetitive (i.e., breech). Currently, not enough data are available to establish the safety of a trial of labor with two or more previous transverse uterine scars.
5. **The answer is B** [IV B 3]. A history of two previous preterm deliveries is the strongest risk factor for spontaneous preterm delivery with a subsequent pregnancy. Premature birth is a risk factor with teenage pregnancies, not advanced maternal age pregnancies. Therapeutic abortions, pyelonephritis, and uterine anomalies are all significant risk factors for spontaneous preterm delivery.
6. **The answer is C** [IV C 5 a]. Pregestational diabetes may increase the risk of birth defects by a factor of three. Anomalies of the heart and central nervous system are the most common problems. The patient with diabetes should be counseled extensively with the aim of achieving good sugar control prior to conception in an attempt to reduce the number of birth defects. Being below ideal body weight does not increase the risk of congenital anomalies. A previous history of intravenous drug use is not significant enough to contribute to congenital anomalies during a current pregnancy. Asthma, hypertension, and liver disease do not increase baseline malformation rate.



Prenatal Screening and Diagnosis: Obstetric Ultrasound and Genetic Testing

EILEEN WANG

I

INTRODUCTION

- A** A **screening** test identifies the risk of a condition and does not definitely confirm a diagnosis. A **diagnostic** test is one where a condition is identified with a “yes” or a “no” answer. Diagnostic tests are usually offered to those with a high risk for a disease, while those at low risk may opt for a screening test before pursuing diagnostic testing. The incidence of a condition, the sensitivity, specificity, and cost of a test and the risk of a procedure are among the factors that can influence the decision to pursue diagnostic versus screening tests. In pregnancy, patients are often stratified into low- or high-risk categories to determine what type of testing they should be offered to ensure the best outcome of their pregnancy. While prenatal testing cannot identify every abnormality a fetus could have, prenatal testing is usually divided into assessment of fetal structure and assessment for genetic abnormalities which may also entail structural abnormalities.
- B** The process of determining risk typically involves:
1. A **detailed history** of the patient, including her age, ethnicity, prior family and obstetrical history (particularly a prior affected child), history of medical conditions, or drug exposures that may impact upon fetal development.
 2. **Genetic counseling** from trained counselors assesses the risks of having a child with a genetic condition or a congenital birth defect and assists the parents in making a decision regarding disease carrier state detection for parents or fetus, prenatal screening and diagnosis, options regarding pregnancy termination, contraception, adoption, and assisted reproductive techniques.
 3. **Presence of ultrasound abnormalities** will potentially increase the risk of chromosomal, syndromic, or structural abnormalities.
 4. **Genetic screening tests** will be reassuring if they predict low risk for a pregnancy while abnormal findings convey high-risk status and may lead to diagnostic testing.
- C** Important general principles for prenatal diagnosis and screening are:
1. The baseline rate of congenital structural abnormalities is 2% to 3% for the general population (low risk).
 2. In general, invasive prenatal diagnostic tests are offered when the risk of having an affected pregnancy is greater than the risks of the procedure, specifically miscarriage. However, in the United States, all reproductive aged women can elect for amniocentesis if desired, including women at low risk for chromosomal abnormalities.
 3. While some genetic carrier screening tests are offered to the general population, such as cystic fibrosis, other may only be offered to those of select backgrounds, for example, Tay–Sachs testing in the Ashkenazi Jewish population.

II

GENETIC SCREENING

A Screening for fetal aneuploidy In the United States, screening or the option of diagnostic testing for fetal aneuploidy should be offered to all women who present for care before 20 weeks of gestation. Previously, amniocentesis and diagnostic testing were reserved only for those with high risk for aneuploidy including those aged 35 years and more at delivery (Table 6–1).

Screening for aneuploidy in pregnancy focuses on evaluating the risks of Down syndrome (DS) and trisomy 18. Several options for screening for aneuploidy are available and the decision to pursue a specific test is based upon gestational age and the ability to obtain the appropriate ultrasound measurements. Typically, a false-positive (FP) rate of 5% is set for these screening modalities—alternatively, the tests can be reported with their best detection rates but with varying FP rates. A set FP rate will also allow for comparison of performance between the different modalities.

1. The **first-trimester screening** includes **nuchal translucency (NT)**, which is the measurement of the size of the fluid collection at the back of the fetal neck (Fig. 6–1) and maternal serum analytes: **maternal serum human chorionic gonadotropin (hCG)** which can be just free β -hCG or the whole hCG molecule, and **pregnancy-associated plasma protein A (PAPP-A)**. NT measurement is used from 11 weeks to 13 6/7 weeks' gestation, and the serum markers are usually drawn at the same time the NT is measured.
 - a. NT measurement (abnormal can be defined as a set cutoff, i.e., 3.5 mm, or compared to gestational age-based cutoffs and frequently is not used alone due to a high FP rate); the detection rate for DS using maternal age and NT is approximately 70%.
 - (1) There are strict guidelines and required certification for NT training to reduce variation and poor technique.
 - (2) An elevated NT may also confer an increased risk for congenital heart defects regardless of the presence or absence of aneuploidy.
 - b. Combined first-trimester screen (NT, PAPP-A, and β -hCG); the detection rate with age and combined first-trimester screening is 80% to 85%.
2. The second-trimester markers include maternal serum α -fetoprotein (**MSAFP**), **hCG**, **unconjugated estriol**, and **inhibin A**. Serum markers are drawn between 15 and 22 weeks' gestation. This is commonly offered when patients enter prenatal care at 14 weeks or later and miss the earlier first-trimester window.
 - a. Triple screen (MSAFP, hCG, and estriol); the detection rate of DS is 60% to 65%.
 - b. Quadruple screen (MSAFP, hCG, estriol, and inhibin A); the detection rate of DS is 70% to 75%.
 - c. With the second-trimester screening, maternal weight, tobacco use, ethnicity, and diabetes are data that are used to modify an individual's risk, as these factors have been shown to shift the medians of the analytes.
 - d. Abnormal analytes may also suggest triploidy or Turner's syndrome.
3. The marker values are adjusted for gestational age by being reported as a multiple of the median for the gestational week that the blood is drawn; the maternal age is incorporated in both the first- and the second-trimester screening to calculate the risk for DS and trisomy 18.
4. Invasive testing (chorionic villus sampling [CVS] in the first trimester and amniocentesis in the second trimester) is offered when the risk for those chromosomal anomalies after the screening test is higher than the risk of the procedure, often a set cutoff such as 1:270 for DS (see section III).

TABLE 6–1 Incidence of Trisomy 21 According to Maternal Age

Maternal Age	Incidence/Live Births
15–19	1/1,250
20–24	1/1,400
25–29	1/1,100
30	1/900
35	1/350
40	1/100
45+	1/25



FIGURE 6–1 Ultrasound showing nuchal translucency, which is the measurement of the size of the fluid collection at the back of the fetal neck.

5. While a first- or a second-trimester screening test may be used alone, the best detection rates for DS result from a combination of the first- and the second-trimester screening.
 - a. Integrated screen (NT, PAPP-A, and quad screen)—[results are disclosed to women only **after the second-trimester portion** of the test is completed]—has the highest detection rates of DS with the lowest FP rates but requires patients to wait for final results. The detection rate of DS with an FP rate of 5% on the basis of the first- and the second-trimester evaluation of risk (FASTER) trial, a large multicenter U.S. trial, was approximately 95%.
 - b. Serum integrated screen (PAPP-A and quad screen)—usually applied when the NT is unobtainable, most commonly due to fetal position; the detection rate of DS from the FASTER trial was approximately 86%.
 - c. Stepwise sequential screen—similar to the integrated screen, but there are preliminary results revealed to the patient after the first-trimester portion of the screen to allow a patient to act upon abnormal results earlier, that is, pursue amniocentesis or CVS, before undergoing the second part; detection rate for DS is about 90% to 95%.
 - d. Contingent sequential screen—if the first-trimester portion shows low risk, the patient will have completed her screening; if the first-trimester risk is elevated, invasive diagnostic testing will be recommended; if the first-trimester risk falls in an intermediate zone then the second-trimester part of the screen is performed. The detection rate for DS ranges from 88% to 94%.
6. Profile of markers associated with aneuploidy
 - a. Risk for DS is elevated in the first trimester if **NT is increased** (alone or in conjunction with the analyte changes), **increased free β -hCG**, **decreased PAPP-A**; in the second trimester, **decreased MSAFP**, **increased hCG**, **decreased estriol**, and **increased inhibin A**.
 - b. Risk for trisomy 18 is increased, if **NT is increased** (alone or in conjunction with the analyte changes) in the first trimester; in the second trimester, **decreased MSAFP**, **decreased hCG**, and **decreased estriol**.
 - c. Trisomy 13 risk is classically not included in these screening modalities.
7. For multiple gestations, NT measurements alone may be the only screening option for fetal aneuploidy, reflecting each fetus. Maternal serum marker screening is not as accurate for twins and is unavailable for triplets. It is difficult to know how much each fetus/placenta directly contributes to serum markers in maternal blood.

B Screening for neural tube defects (NTDs; technically a structural issue but frequently included with genetic screening since MSAFP from the second-trimester screen is utilized).

1. The second-trimester MSAFP can screen for risk of NTD, while ultrasound can directly visualize an NTD or associated intracranial changes.
2. Both have sensitivity (detection rate) of 80% to 90% for open NTDs. Amniocentesis can be performed to directly measure amniotic fluid AFP.

TABLE 6–2 Conditions Characterized by Elevated α -Fetoprotein

Multiple gestation	Fetal death
Bladder exstrophy	Cystic hygroma
Congenital nephrosis	Aneuploidy
Fetal bowel obstruction	Sacroccygeal teratoma
Underestimated gestational age (most common explanation)	
Abdominal wall defects (omphalocele and gastroschisis)	

3. If the first-trimester screening for aneuploidy or CVS is performed or if screening for aneuploidy is declined, MSAFP alone should be offered.
4. MSAFP can be performed from 15 to 22 weeks' gestation.
 - a. An **elevated value** is indicative of an increased risk for an NTD and other disorders (Table 6–2).
 - b. A **low value** is indicative of an increased risk for DS.

C Screening of single gene mutations Ultimately screening is optional. Both parents should be tested ideally; and usually all mutations cannot be identified.

1. **Cystic fibrosis** is the most common inherited disorder in Caucasians. **The carrier rate is 1 in 25 non-Hispanic Caucasians.** It has an **autosomal recessive** inheritance pattern. Prenatal diagnosis should be offered if both parents are carriers.
 - a. Screening can be offered to all parents regardless of ethnicity, but should be offered when familial history is positive for cystic fibrosis and to all couples when both partners are of Caucasian, European, or Ashkenazi Jewish ancestry.
 - b. The most common mutation is the δ -F508, which accounts for approximately 70% of mutations found in Caucasians.
 - c. Most laboratories screen for 25 mutations, which account for more than 80% of mutations found in Caucasians; more than 90% mutations can be found in the Ashkenazi Jewish population.
2. **Hemoglobinopathies.** There are approximately 2 to 2.5 million people in the United States with inherited abnormalities of hemoglobin. **Normal hemoglobin** is composed of three types of hemoglobin. **Hemoglobin A** has two α -chains and two β -chains and makes up 95% of adult hemoglobin. **Hemoglobin A₂** has two α -chains and two δ -chains and makes up 2% to 3.5% of adult hemoglobin. **Hemoglobin F** has two α -chains and two γ -chains and makes up the remainder of adult hemoglobin.
 - a. **Sickle cell screening.** All people of African descent should undergo carrier screening for sickle cell with a **hemoglobin electrophoresis**. Sickle cell disease has an **autosomal recessive** inheritance pattern.
 - (1) Prenatal diagnosis should be offered if both parents are carriers of either sickle cell trait or another hemoglobinopathy such as hemoglobin C trait or β -thalassemia since a child may have sickle-thalassemia hemoglobin and be very symptomatic.
 - (2) The frequency of sickle cell trait in the African American population is approximately 1 in 12.
 - (3) **Sickle hemoglobin (Hb S)** occurs when glutamic acid is replaced by valine at the sixth position in the β -globin chain. Hb S functions normally in the oxygenated state. In the deoxygenated state, hydrophobic bonds are formed, which cause red blood cell distortion, or sickling. This leads to vaso-occlusion, tissue infarction, and anemia.
 - b. **Thalassemias.** Patients of Southeast Asian or Mediterranean descent should be offered carrier screening with a complete blood count. When the mean corpuscular volume (MCV) is low (less than 80 fL) with normal iron studies, a hemoglobin electrophoresis should be performed.
 - (1) α -Thalassemia
 - (a) Groups at risk are of Southeast Asian, West Indian, Mediterranean, and African descent.
 - (b) Production of the α -globin chains is decreased.

- (c) DNA-based testing is needed to detect α -globin gene deletion. (When MCV is low and iron studies are normal, Hb electrophoresis is not helpful since the different types of Hb will stay in proportion with each other.)
- (2) β -Thalassemia
 - (a) Groups at risk are from Mediterranean, Asian, Middle Eastern, Hispanic, and West Indian descent.
 - (b) Production of the β -globin chains is decreased.
 - (c) Elevated Hb A₂ (more than 3.5%) on Hb electrophoresis is suggestive of β -thalassemia.
- 3. **Ashkenazi Jewish carrier screening.** Currently as recommended by the American Congress of Obstetricians and Gynecologists (ACOG), **cystic fibrosis** (see II C1), **Tay-Sachs disease**, **Canavan disease**, **familial dysautonomia**. These are **autosomal recessive** conditions.
 - a. **Tay-Sachs disease** is due to the absence of the enzyme **hexosaminidase A**, which leads to accumulation of GM₂ gangliosides, resulting in a severe progressive neurologic disease causing death in early childhood. Prenatal diagnosis should be offered if both parents are carriers. The carrier rate is 1 in 30 in Ashkenazi Jews and 1 in 300 in those of non-Jewish descent. Carrier screening should be offered if there is a positive familial history, to couples where both members are of Ashkenazi Jewish, French-Canadian, or Cajun descent, and in some cases when only one member is of high-risk descent.
 - b. **Canavan disease** results from a deficiency of the aspartoacyclase enzyme affecting the central nervous system with developmental delay, hypotonia, seizures, resulting in early death. The carrier frequency in this population is 1 in 40.
 - c. **Familial dysautonomia** leads to difficulties with feeding, sweating, blood pressure control, pain, and temperature insensitivity; the carrier rate is 1:32.
 - d. Other single gene recessive conditions seen in the Ashkenazi Jewish population that are available for screening include mucopolipidosis IV, Niemann-Pick disease type A, Fanconi anemia group C, Bloom syndrome, and Gaucher disease.
- 4. **Spinal muscular atrophy** is a recessive condition that impacts the spinal motor neurons, leading to weakness and muscle atrophy. There is a mutation in the survival motor neuron gene (SMN1). The carrier frequency is 1/40 to 1/60. There are three types, of which only type I leads to early infant death. The American College of Medical Genetics recommends offering screening to all patients. ACOG recommends counseling and offering screening only to those who have family histories or request testing after appropriate counseling.

III

PRENATAL DIAGNOSIS TECHNIQUES

- A** **Ultrasound** uses low-energy high-frequency sound waves (often from 3 to 5 Mhz) and is the most common noninvasive diagnostic technique used in pregnancy. It is felt to be safe in pregnancy with no direct associations with adverse pregnancy or fetal outcomes in humans to date. The ALARA (as low as reasonably achievable) principle is applied such that most ultrasound machines use settings with energy levels below the levels considered safe in pregnancy.
 - 1. Ultrasound examinations will provide different information according to the gestational age at which they are done.
 - a. Fetal anatomy is best evaluated during the second trimester, and most routine ultrasounds are performed at that time.
 - b. Accurate determination of gestational age is best obtained with a first-trimester ultrasound examination.
 - c. The third-trimester ultrasound examinations are ordered on a routine basis (for fetal weight estimation and detection of **growth** abnormalities), but most are performed for specific indications.
 - 2. The **first-trimester ultrasound** can be performed using transvaginal (with clearer visualization of early structures) or transabdominal approaches.
 - a. Indications are focused on **viability** and **location** of pregnancy and include the following:
 - (1) Confirm the presence of an intrauterine pregnancy
 - (2) Estimate gestational (menstrual) age
 - (3) Define the cause of vaginal bleeding



FIGURE 6–2 Ultrasound showing measurement of the fetal CRL during the first trimester.

- (4) Evaluate pelvic pain
- (5) Evaluate a suspected ectopic pregnancy
- (6) Diagnose or evaluate multiple gestations
- (7) Confirm cardiac activity
- b. A first-trimester scan should document specific findings:
 - (1) Location of the gestational sac. An intrauterine sac is visible transvaginally as early as 5 weeks' gestation.
 - (2) Fetal number (chorionicity).
 - (3) Fetal viability. Fetal cardiac activity should be detected transvaginally when the embryo is 5 mm or more in length (approximately 6 weeks' gestation).
 - (4) Gestational age. Measurement of the fetal crown–rump length (CRL) between 6 and 13 weeks' gestation can estimate fetal age within 5 days (Fig. 6–2).
 - (5) The uterus and adnexal structures.
 - (6) The NT when done as part of screening for aneuploidy and only after adequate counseling.
3. The second- and the third-trimester ultrasounds are typically performed transabdominally. Certain criteria are expected to be assessed in these studies.
 - a. Fetal life, number, presentation
 - (1) If multiples—number of sacs, placentas, dividing membrane, fetal sizes, fluid volume
 - b. Estimate of amniotic fluid volume
 - c. Placental location, appearance, relation to cervical os (evaluation for previa)
 - d. Evaluation of uterus, adnexa, cervix if possible
 - e. Fetal anatomy
 - f. Fetal biometry
4. While the primary indication for the second-trimester ultrasound is the **fetal anatomy survey**, the following are indications for ultrasound outside the first trimester:
 - a. Evaluation of gestational age (particularly with late entry to prenatal care)
 - b. Assessment of fetal viability
 - c. Evaluation of multiple gestation
 - d. Screening for fetal anomalies, especially in the presence of an abnormal multiple marker screen or MSAFP
 - e. Evaluation and follow-up of fetal growth and size
 - f. Vaginal bleeding of undetermined etiology
 - g. Evaluation of cervical length (using transvaginal scanning)
 - h. Suspected amniotic fluid abnormalities (oligohydramnios or polyhydramnios)
 - i. Assessment of fetal well-being (i.e., biophysical profile)
 - j. Determination of fetal presentation
 - k. Guidance during procedures: CVS (first trimester), amniocentesis, version, percutaneous umbilical blood sampling (PUBS)
 - l. Evaluation for ectopic pregnancy and molar pregnancy
 - m. Evaluation of pelvic mass

- n. History of previous congenital anomaly
 - o. Follow-up evaluation of a fetal anomaly
 - p. Follow-up evaluation of placental location for suspected placenta previa
5. Fetal anatomy survey is typically done at 18 to 20 weeks at a time and typically includes, but is not limited to the following:
 - a. Head and neck—Cerebral ventricles/choroid plexus/cerebellum/cisterna magna/midline falx/cavum septum pellucidum
 - b. Chest—Four-chamber heart/outflow tracts if technically feasible
 - c. Abdomen—Stomach (size, position, presence)/kidneys/bladder/cord insertion/three-vessel cord/anterior abdominal wall
 - d. Spine (cervical, thoracic, lumbosacral)
 - e. Extremities (legs and arms)
 - f. Gender (only medically indicated if multiple gestation)
 - g. Fetal anatomy may not be visualized due to fetal position, maternal body habitus, late or early gestational age, or low amniotic fluid levels
 6. Fetal **biometry** will assess growth if gestational dating is known, but if dating is unknown biometry will be used to assign gestational age.
 - a. The **biparietal diameter** is measured at the level of the thalamus and the cavum septum pellucidum. The biparietal diameter is the most accurate measurement of gestational age between 12 and 18 weeks' gestation (Fig. 6–3).
 - b. The **head circumference** is measured at the same level as the biparietal diameter.
 - c. The **abdominal circumference** is measured on a true transverse view at the level of the stomach and the umbilical vein entering the liver.
 - d. The long axis of the femur shaft is measured for the **femur length**.
 7. **Estimated fetal weight (EFW)** may be estimated using various combinations of biparietal diameter, head circumference, femur length, and abdominal circumference in different formulae. The EFW in the third trimester may have an error rate of $\pm 15\%$ of the EFW. The frequency of growth scan should be no closer than 2 weeks since the variation of measurements may represent inter-observer differences if a shorter time frame is used.
 - a. If the EFW is below the tenth percentile for the gestational age, the fetus is small for gestational age (SGA) and intrauterine growth restriction (IUGR) is suspected.
 - b. If the EFW is above the 90th percentile for the gestational age, the fetus is large for gestational age (LGA) and macrosomia is suspected.
 8. **Amniotic fluid volume** can be assessed by semi-quantitative methods.
 - a. Measurement of the deepest single pocket of amniotic fluid
 - (1) There is oligohydramnios if the pocket is less than 2 cm vertically.
 - (2) The amniotic fluid volume is adequate if the pocket measures 2 to 8 cm vertically.



FIGURE 6–3 Ultrasound showing measurement of the biparietal diameter. This is measured at the level of the thalamus and the cavum septum pellucidum.

TABLE 6–3 Fetal Malformations Associated with Polyhydramnios**Central Nervous System**

Anencephaly
Hydrocephaly
Encephalocele

Gastrointestinal System

Gastroschisis
Omphalocele
Esophageal atresia
Duodenal atresia
Diaphragmatic hernia

Respiratory System

Cystic adenomatoid malformation of the lung
Chylothorax

Musculoskeletal System

Myotonic dystrophy
Skeletal dysplasia

(3) There is polyhydramnios if a pocket measures more than 8 cm vertically. Polyhydramnios is associated with a higher incidence of congenital abnormalities (Table 6–3).

- b. The amniotic fluid index is calculated by adding together the measurements of the vertical depths of amniotic fluid in the four quadrants using the maternal umbilicus as the crux of the four quadrants of the uterus. Normal values are between 5 cm and 25 cm or may be defined by gestational age.

9. **Fetal well-being for those fetuses at higher risk of stillbirth** can be assessed with the **biophysical profile** which is composed of:

- a. Amniotic fluid volume
- b. Fetal tone
- c. Fetal movements
- d. Fetal breathing
- e. Nonstress test
- f. A score of 2 (normal) or 0 (abnormal) is assigned to each component. A total score of 8 or 10 is reassuring. A total score of less than 8 is abnormal and is managed according to the gestational age and the clinical situation, with a score of 0 or 2 very concerning for imminent fetal death

B Fetal echocardiography is a detailed ultrasound examination of the heart. It performed to detect, diagnosis, and serially evaluate congenital heart defects (CHDs) and fetal arrhythmias. It is usually performed between 20 and 22 weeks' gestation and its indications include:

1. Risk factors for CHD (familial history of CHD, maternal diabetes, exposure to cardiac teratogens)
2. Suspected CHDs on regular ultrasound examination or an elevated NT in the first trimester
3. Suspected fetal arrhythmia on ultrasound or auscultated in the office
4. Other congenital anomalies detected on regular ultrasound examination
5. Nonimmune hydrops fetalis

C Amniocentesis is a transabdominal aspiration of amniotic fluid (usually 10 to 30 mL) under ultrasound guidance using a 20- to 22-gauge needle. It is imperative that Rh-negative women who are not sensitized receive **Rho(D) immune globulin** after the procedure. The amniotic fluid contains fetal cells, which can be cultured and evaluated for chromosomal abnormalities and molecular testing. Specific proteins and hormones can also be identified or measured in the amniotic fluid.

1. **Genetic amniocentesis** is usually performed from 15 to 18 weeks' gestation, a time when diagnostic tests can be performed, and elective termination is available if the patient desires it after receiving the diagnostic information.
 - a. The **risk of fetal loss** from a second-trimester amniocentesis is **0.2% to 0.5%**.
 - b. Amniotic fluid can be assessed for α -fetoprotein) and acetylcholinesterase levels in the evaluation of NTDs (if elevated can identify >95% of open NTDs).
 - c. Amniotic fluid can be used to test for the presence of infection such as cytomegalovirus, parvovirus, toxoplasmosis, usually by polymerase chain reaction (PCR) or culture.

2. Amniocentesis can also be done later in pregnancy for other indications including:
 - a. Measuring **bilirubin** in the amniotic fluid by spectrophotometry, which reflects fetal hemolysis and indirectly evaluates the degree of fetal anemia. It is used in the management of alloimmunization. More commonly, non-invasive ultrasound evaluation of the middle cerebral artery Doppler flow in the fetus is now used to screen for fetal anemia with isoimmunization.
 - b. Evaluation of **fetal lung maturity** is performed using the lecithin-to-sphingomyelin (L/S) ratio and the presence of phosphatidyl glycerol (PG) or can be assessed by the surfactant-albumin ratio using fluorescence polarization (TDX-FLM II).
 - c. Diagnosis of in utero **infections** as noted above if maternal infection has been documented or fetal infection is suspected on ultrasound examination.
 - d. The risk of preterm delivery from a third-trimester amniocentesis is **1% to 2%**.

D Chorionic villus sampling is typically performed at 10 to 12 weeks' gestation. Fetal cells can be obtained either by a transabdominal or transcervical approach and is ultrasound guided. The major benefit of this procedure is earlier prenatal diagnosis.

1. The risk of fetal loss from the procedure is 1%.
2. The accuracy is comparable to that of amniocentesis.
3. Chromosomal analysis and fetal DNA analysis are possible; however, amniotic fluid levels of markers such as AFP cannot be measured with this method. Confined placental mosaicism is a rare finding where there are two or more karyotypically different cell lines seen but it may not be seen in the fetus. Careful genetic counseling is needed and amniocentesis or percutaneous blood sampling maybe recommended.
4. Limb reduction defects have been associated with this procedure, which may have been related to very early procedures before 10 weeks.
5. Rh-negative women must receive Rho(D) immune globulin after the procedure.

E Other techniques

1. **Percutaneous umbilical blood sampling** or cordocentesis is used to sample fetal blood for karyotype, DNA-based analysis, hemoglobin electrophoresis, and diagnosis of fetal infection, anemia, or thrombocytopenia.
 - a. It must be performed under ultrasound guidance much like an amniocentesis but with direct needle placement into the umbilical cord, typically at the placental cord insertion.
 - b. The **risk of fetal loss** from the procedure is reported as **1% to 3%**, but varies greatly according to the indication.
 - c. Rh-negative women must receive Rho(D) immune globulin after the procedure.
 - d. In cases of fetal anemia, the needle may then be used to transfuse O-negative, CMV-negative, irradiated blood to the fetus.
2. **Preimplantation diagnosis** requires the use of in vitro fertilization techniques such that one cell from the early embryo or a polar body is extracted and assessment of (usually) a single gene disorder is then performed. It is not recommended for screening for aneuploidy (abnormal chromosome number) and has limitations since only one cell is tested.
3. **Fetal skin sampling** can be performed to obtain fetal cells, usually to diagnose severe skin conditions such as epidermolysis bullosa.

F From the cells acquired from these different techniques, **chromosomal abnormalities** such as DS (trisomy 21), trisomy 18, trisomy 13, triploidy, Turner syndrome (45, XO), and Klinefelter (47, XXY) can be identified using different studies.

1. **Karyotype** is obtained from cultured cells, and chromosomes are counted and analyzed for structural alterations, but cannot identify smaller alterations (less than 3 Mb [million base pairs]) and requires dividing cells (and may take up to 2 weeks to complete).
2. Fluorescence in situ hybridization (**FISH**), by using targeted DNA probes can be used for more **rapid** identification (i.e., 1 to 3 days) of specific abnormalities, chromosomal or alterations less than 3 MB, but due to technical reasons only can test for limited abnormalities, typically evaluating for chromosome 13, 18, 21, X, and Y.

3. **DNA of the fetus can be retrieved and tested** for specific diseases.
 - a. If the precise molecular basis of the disease is known, such as in sickle cell, DNA techniques like allele-specific hybridization and PCR-based studies can be used to identify the condition.
 - b. If the precise molecular basis of the disease is not known, prenatal diagnosis is still possible in a given family using **restriction fragment length polymorphisms (RFLPs)**. Restriction endonucleases are used to cleave homologous DNA sequences resulting in DNA fragments of different lengths which are then hybridized to a specific DNA probe and then gel electrophoresis is applied. The resulting pattern is compared among subjects.
 - c. DNA can also be analyzed (without the need of dividing cells) with **array comparative genomic hybridization (CGH)**, which can identify mutations less than 3 Mb across the human genome, but will also detect benign alterations as well; therefore, since all syndromic and structural abnormalities have not been mapped out it may be difficult to assign meaning to some of these alterations. CGH will miss balanced translocations and inversions. Strict genetic counseling pretesting and posttesting is required. This is NOT currently being offered to all abnormal cases.

IV

INDICATIONS FOR PRENATAL DIAGNOSIS

A High risk for chromosomal abnormalities

1. Positive screening for fetal aneuploidy (see III A)
2. Advanced maternal age (i.e., at least 35 years at the time of delivery) (see Table 6–1) but younger women may elect this as well
3. A previously affected child
4. Either parent has a chromosomal translocation or inversion
5. Abnormal ultrasound findings
 - a. **Congenital malformations** involving a major organ or system
 - (1) **Congenital heart defects** are the most common congenital malformation and occur in 8 per 1,000 live births.
 - (2) They tend to have a multifactorial inheritance pattern; though the 22q11 microdeletion of DiGeorge syndrome is associated with conotruncal abnormalities.
 - (3) Risk factors include familial history of congenital heart defects, pregestational maternal diabetes, maternal rubella infection during the first trimester, and exposure to teratogens such as alcohol and some antiepileptic medications.
 - b. **NTDs** are one of the most common congenital malformations and occur in 1 to 2 per 1,000 live births (Fig. 6–4).



FIGURE 6–4 This image reveals a fetus with anencephaly, the most extreme form of an NTD. The asterisk denotes the orbit with no apparent cranium above.

- (1) They have a multifactorial inheritance pattern.
 - (2) Risk factors include familial history of NTDs, pregestational maternal diabetes, maternal seizure disorder, and maternal intake of some antiseizure medications.
 - (3) NTD incidence can be reduced by maternal **folic acid supplementation** at least 3 months prior to conception and during the first 3 months of pregnancy. A 0.4-mg dose daily will reduce the incidence of NTDs in the general population by 50%. A 4-mg dose daily will reduce the recurrence risk in women with a previous affected child by 70%.
- c. **Markers** for aneuploidy, ultrasound findings that can be seen in normal fetuses but are observed with an increased frequency in fetuses with chromosomal abnormalities.
- (1) Increased nuchal thickness, even isolated, is an indication for invasive prenatal diagnosis.
 - (2) Pyelectasis (dilated renal pelvis), choroid plexus cyst, short femur, and humerus warrant a detailed ultrasound examination to search for anomalies and other markers but may not require invasive prenatal diagnosis if they are an isolated finding.

B Mendelian abnormalities

1. Inborn errors of metabolism

- a. Mucopolysaccharidoses
- b. Mucopolipidoses
- c. Lipidoses
- d. Amino acid disorders
- e. Miscellaneous biochemical disorders

2. Abnormalities in DNA structure. Examples include congenital adrenal hyperplasia; Gaucher disease; Ehlers–Danlos types IV, VI, and VII; Niemann–Pick disease; osteogenesis imperfecta congenita; and xeroderma pigmentosum.

C Abnormal maternal serum α -fetoprotein (MSAFP) which may indicate risk for DS or risk for open NTD.

D Fragile X syndrome is the most common cause of inherited mental retardation.

1. It has an **X-linked** inheritance pattern based on amplification of a CGG trinucleotide repeat in the fragile X mental retardation 1 (FMR-1) gene inherited from the oocyte; women can have a number of premutation repeats (55 to 200) which in the fetus amplify into the full mutation of repeats (>200). Males present with more significant findings, while females tend to exhibit milder abnormalities, which is thought to be due to lyonization (with random inactivation of one of the two X chromosomes).
2. Women who have a child with or a familial history of mental retardation or developmental delay should be tested to see if they carry the premutation and should be offered prenatal diagnosis if they do.
3. Women who carry the premutation are at risk for developing premature ovarian failure and may therefore have difficulties conceiving.



Study Questions for Chapter 6

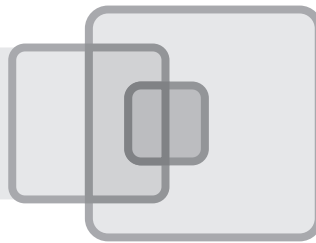
Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. Which combination of markers is suggestive of DS?
 - ☐ A Small NT, normal PAPP-A, normal β -hCG
 - ☐ B low MSAFP, low hCG, low estriol, low inhibin A
 - ☐ C very high MSAFP, high hCG, normal estriol, high inhibin A
 - ☐ D low MSAFP, high hCG, low estriol, high inhibin A
 - ☐ E high MSAFP, normal hCG, normal estriol, and normal inhibin A
2. Which of the following cannot be detected on a second-trimester ultrasound examination?
 - ☐ A Anencephaly
 - ☐ B Renal agenesis
 - ☐ C Sickle cell disease
 - ☐ D Two-vessel cord
 - ☐ E Tetralogy of Fallot
3. A newly married 22-year-old woman of Jewish descent, gravida 0, comes to see you for genetic counseling referred by her family doctor. Which of the following is most appropriate to offer the patient after specific counseling?
 - ☐ A Discussion with husband to review his family history and pursuing carrier testing for cystic fibrosis, Canavan disease, Tay–Sachs, and familial dysautonomia
 - ☐ B Fetal chromosome analysis after patient has achieved pregnancy
 - ☐ C Carrier screening for cystic fibrosis, Gaucher disease, α -thalassemia
 - ☐ D Paternal hemoglobin electrophoresis
 - ☐ E Comparative genomic hybridization of the patient's blood sample
4. Which of the following procedures poses the lowest risk for fetal loss?
 - ☐ A Chorionic villus sampling
 - ☐ B Fetal skin sampling
 - ☐ C Percutaneous umbilical blood sampling
 - ☐ D Fetal echocardiography
 - ☐ E Amniocentesis
5. Which of the following is NOT an indication for prenatal diagnosis?
 - ☐ A Omphalocele detected on a second-trimester ultrasound
 - ☐ B Elevated MSAFP
 - ☐ C Previous child with cystic fibrosis
 - ☐ D Maternal ventricular septal defect (VSD)
 - ☐ E Prior infant delivered at 34 weeks due to spontaneous preterm labor



Answers and Explanations

1. **The answer is D** [II A 6]. The risk for DS is increased when AFP and estriol levels are lower than normal and hCG and inhibin A levels are higher than normal. Choice A is associated with a negative first-trimester screen. B reflects a trisomy 18 pattern for the second-trimester screening. C is associated with a triploidy picture. E is a pattern that can be seen with open NTD.
2. **The answer is C** [III A 4]. The fetal anatomic survey should include views of the head, spine, thorax, heart, stomach, kidney, bladder, umbilical cord, abdominal wall, and extremities. It can detect anomalies such as anencephaly, congenital heart defects, renal agenesis, or two-vessel cord. Prenatal diagnosis of sickle cell disease can only be performed using invasive methods (CVS or amniocentesis) to obtain fetal DNA and it does not have overt structural findings that can be seen on ultrasound.
3. **The answer is A** [II C 3]. Certainly due to the patient's Jewish background the counseling should entail offering Jewish carrier screening, but since these are recessive traits it is important to determine the husbands/future father's genetic background as well to determine if he too will need carrier testing. Choice B is not appropriate as this is a diagnostic test directly on the pregnancy which may not be needed if the parents are not carriers. Answer C could be possible, but is not the best choice because while cystic fibrosis and Gaucher disease do occur in greater frequency in the Jewish population, α -thalassemia studies are usually triggered by low MCV and normal iron studies. D may have some relevance should the patient actually have a hemoglobinopathy trait, but this is not recommended routinely of patients who are of Jewish descent. E is not recommended due to the complexity of interpreting CGH in an otherwise healthy patient.
4. **The answer is D** [III C–E]. Fetal echocardiography is a noninvasive diagnostic procedure and thus does not carry any fetal loss risk. Amniocentesis has a 0.25% to 0.5% fetal loss rate. CVS has a 1% fetal loss rate. Percutaneous umbilical blood sampling carries a 1% to 3% loss rate. Fetal skin biopsy is an invasive procedure much like an amniocentesis.
5. **The answer is E** [IV A–E]. Spontaneous preterm labor with resulting phenotypically normal infant is not an indication for prenatal diagnosis. Elevated MSAFP indicates an increased risk for NTDs and other anomalies and further testing should be offered. With a previous child affected with cystic fibrosis, the recurrence risk is 25%. Familial history of CHDs is a risk factor for CHDs, and fetal echocardiography should be offered. Omphalocele is associated with chromosomal anomalies and other congenital malformations.



Teratology

NADAV SCHWARTZ

I

INTRODUCTION

Teratology is the **study of abnormal fetal development**. Major birth defects occur in approximately 3% of all deliveries. A teratogenic agent, which can be identified in less than 50% of the cases, is any chemical (drug), infection, physical condition, or deficiency that, on fetal exposure, can alter fetal morphology or subsequent function. Teratogenicity appears to be related to the developmental stage of the fetus at the time of exposure and the route and length of administration of the teratogen. In addition, a genetic predisposition likely plays a role in many cases. Because any woman in her reproductive years may be pregnant, all women should be made aware of the teratogenic potential associated with medications she is taking. In cases of known teratogens, women and their physicians have a responsibility to effectively prevent pregnancy with adequate contraceptive methods. Preconception counseling for women on potential teratogens who are contemplating pregnancy can be useful in minimizing or avoiding teratogenic exposure in pregnancy.

A Definition Teratogenicity of an agent or factor is defined by the following criteria:

1. **Presence of the agent during the critical period of development when the anomaly is likely to appear.** Malformations are caused by intrinsic problems within the developing tissues at a specific time in organogenesis.
2. **Production of the anomaly in experimental animals when the agent is administered during a stage of organogenesis similar to that of humans.** Teratogenicity may not become apparent for several years; for example, in utero exposure to diethylstilbestrol was shown to cause genital tract abnormalities, such as adenosis and carcinoma, but these abnormalities did not become apparent until the offspring reached the reproductive years.
3. **Ability of the agent to act on the embryo or fetus either directly or indirectly through the placenta.** For example, heparin is not teratogenic because, unlike warfarin, it cannot cross the placenta because of its large molecular weight.

B Structural defects have been categorized into three groups:

1. **Malformations** are morphologic defects of an organ or other part of the body resulting from an abnormality in the process of development in the first trimester. This leads to incomplete or aberrant morphogenesis (e.g., ventricular septal defect).
2. **Deformations** are abnormal forms, shapes, or positions of a body part caused by constraint within the uterus, usually occurring in the second or third trimester. An example is clubfeet from oligohydramnios.
3. **Disruptions** are defects from interference with a normally developing organ system, usually occurring after organogenesis. An example is amniotic band syndrome with resultant limb defects.

C Developmental stage at time of exposure Susceptibility of the conceptus to teratogenic agents depends on the developmental stage at the time of exposure (Fig. 7–1).

1. **Resistant period.** From Days 0 to 11 of gestation (postovulation), the fetus exhibits the “all or none” phenomenon with regard to major anomalies; that is, it will either be killed by the insult or survive unaffected. This is the period of predifferentiation when the aggregate of totipotent cells can recover from an injury and continue to multiply.

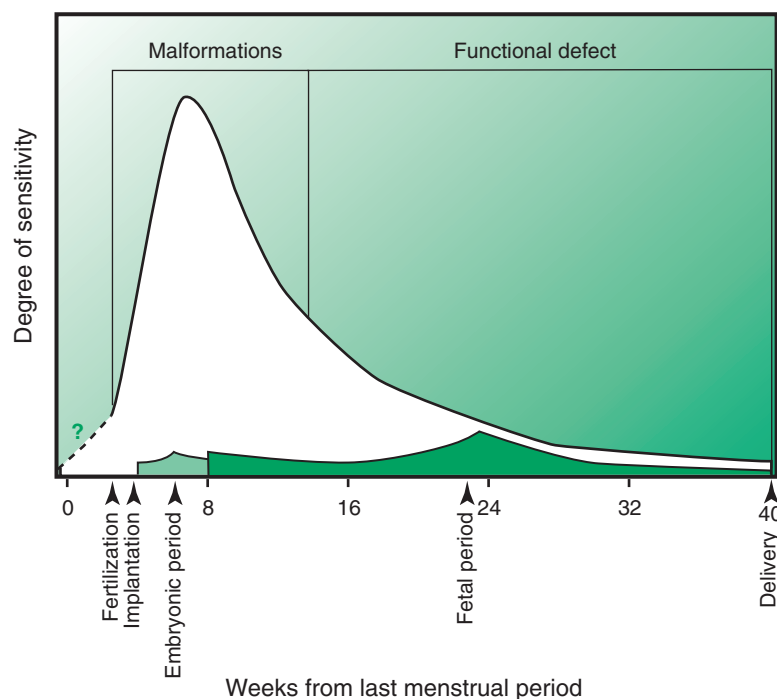


FIGURE 7-1 Embryonic and fetal sensitivity to environmental influences as a function of developmental state. (Reprinted with permission from Creasy RK, Resnik R. *Maternal-Fetal Medicine: Principles and Practice*. Philadelphia: WB Saunders, 1984:95).

2. **Maximum susceptibility (embryonic period).** From Days 11 to 57 of gestation, the fetus is undergoing organ differentiation and, at this time, is most susceptible to the adverse effects of teratogens. The particular malformation depends on the time of exposure. After a certain time in organogenesis, it is thought that abnormal embryogenesis can no longer occur. For example, because the neural tube closes between Days 22 and 28 postconception (5 weeks after the last menstrual period), a teratogen must be active before or during this period to initiate development of a neural tube defect (e.g., spina bifida or anencephaly).
3. **Lowered susceptibility (fetal period).** After 57 days (8 weeks) of gestation, the organs have formed and are increasing in size. A teratogen at this stage may cause a reduction in cell size and number, which is manifested by:
 - a. Growth retardation
 - b. Reduction of organ size
 - c. Functional derangements of organ systems

D Administration of teratogen The route and length of administration of a teratogen alter the type and severity of the malformation produced. Abnormal developments increase in frequency and degree as the dosage increases. Furthermore, polypharmacy with several potential teratogens increases the risk of a birth defect. For example, the use of multiple antiseizure medications to control a woman's seizure disorder places the pregnancy at significantly increased risk of birth defects (e.g., neural tube defects) compared to women controlled on monotherapy. This is another area where preconception counseling to reduce medication exposure to the lowest effective regimen can reduce the risk to the fetus.

E Genetic susceptibility In some cases, it is clear that teratogen exposure is not the sole requirement for the fetus to be affected. While other environmental factors are likely at play, there are several examples where a clear genetic susceptibility has been identified to increase the risk of teratogenicity in an exposed fetus. One example is the variability in epoxide hydrolase activity in patients with different genetic polymorphisms. Low enzyme levels have been associated with an increased risk of teratogenicity in pregnancies exposed to phenytoin.

II

TERATOGENIC AGENTS

A Ionizing radiation The dose of radiation and the gestational age during exposure are predictive of the adverse neonatal effects: microcephaly, mental retardation, and growth retardation. For example, the in utero victims of the atomic explosions in Hiroshima and Nagasaki have suffered from both birth defects and leukemia. However, follow-up studies have shown that most children with these adverse effects were those exposed before 15 weeks' gestation, during the period of organogenesis, whereas most of the children exposed during the third trimester had growth retardation but normal intelligence.

1. **Time of exposure.** Fetal effects depend on the gestational age (postovulation) at the time of exposure.
 - a. At 2 to 4 weeks, either the fetus is normal or a spontaneous abortion occurs.
 - b. At 4 to 12 weeks, microcephaly, mental retardation, cataracts, growth retardation, or microphthalmia may occur.
 - c. At 12 to 16 weeks, mental retardation or growth retardation occurs.
 - d. After 20 weeks, the effects are the same as with postnatal exposure and include hair loss, skin lesions, and bone marrow suppression.
2. **Dose effect**
 - a. After exposure to less than 5 rad, and probably less than 10 rad, an adverse fetal outcome is unlikely to result.
 - b. After exposure to 10 to 25 rad, some adverse fetal effects may result.
 - c. After exposure to more than 25 rad, classic fetal effects, including growth retardation, structural malformations, and fetal resorption, may be detected. At this level of exposure, elective abortion should be offered as an option.
3. **Risk of malignancy.** In addition to fetal anomalies, significant radiation exposure to the fetus has been associated with an increase in childhood leukemia. However, in general, the absolute risk remains small with the incidence being 1 in 2,000 in exposed children compared to 1:3,000 in unexposed children.
4. **Diagnostic radiation.** Estimated radiation exposures for common diagnostic radiology tests are shown in Table 7-1. It is important to note that no single diagnostic radiology tests reaches the 5-rad threshold currently used as the minimum dose needed to increase the risk of fetal anomalies. However, given the variety in CT scan protocols and machines, it may be wise to obtain the estimates at the individual institution. Radiation physicists can be consulted to help obtain accurate estimates.
5. **Fluoroscopic procedures.** There are several procedures commonly performed under fluoroscopic visualization, such as endoscopic retrograde cholangiopancreatography (ERCP) and angiograms. Attempts to minimize the use of fluoroscopy to the abdomen and pelvis, as well as abdominal shielding can reduce the fetal exposure. However, given the variability in the time and

TABLE 7-1 Fetal Radiation Exposure for Common Radiologic Tests

Test	Dose (Rads)
Chest X-ray	<0.0007
Abdominal series	0.2–0.3
Mammogram	0.01–0.02
Head CT	<0.05
Chest CT	0.01–0.2
Abdominal CT	0.8–3
Upper GI series	0.05–0.1
Barium enema	0.3–4
VQ scan	<0.4
HIDA scan	0.15
Intravenous pyelogram	0.68–1.4
CT pelvimetry	0.25

amount of fluoroscopy use, consultation with a radiation physicist should be considered to help ensure accurate patient counseling.

6. **Radiation therapy.** Radiation doses are significantly higher when therapeutic radiation, such as for cancer treatment is being used. Thus, radiation therapy is generally contraindicated in pregnancy.
7. **Radioactive iodine.** In addition to the radiation risk from radioactive iodine used in thyroid disease, the iodine can concentrate in the fetal thyroid after ~10 weeks of gestation and lead to fetal thyroid dysfunction. Thus, radioactive iodine should not be used in pregnancy.

B Drugs and medications In the United States, surveys show that 45% to 95% of pregnant women ingest either over-the-counter or prescription drugs other than iron and vitamins during their pregnancy. Many are taken before a woman realizes that she is pregnant or are taken without the advice of a physician. Physicians caring for women of childbearing age should be aware of potential teratogenicity of medications and should be able to address questions arising from the accidental or intentional ingestion of drugs during pregnancy.

1. Approximately, 3% to 5% of newborns have congenital malformations caused by a host of environmental and genetic factors. Drugs and medications account for less than 1% of these malformations.
2. Access to the fetoplacental unit is critical in the causation of developmental anomalies. Factors affecting access of the drug or medication to the fetus include:
 - a. Maternal absorption
 - b. Drug metabolism
 - c. Protein binding and storage
 - d. Molecular size (molecules with a molecular weight of more than 1,000 Da do not cross the placenta easily)
 - e. Electrical charge
 - f. Lipid solubility
3. Animal research can help identify teratogenic potential and such research is often used to provide evidence of safety. In fact, animal research is used in the definitions of the FDA drug classification system (Table 7–2).

However, due to species variation, animal research has the potential to lead to erroneous information. The most striking example is **thalidomide**, in which exposure in mice and rats failed to produce limb defects but caused severe limb reduction defects in humans, monkeys, and rabbits. On the other hand, every drug found to be teratogenic in humans has subsequently been shown to cause similar defects in some animals, although species variation exists. It is worth noting that drugs that cause teratogenesis in animals often do so at much higher doses than used clinically in humans, where similar outcomes are not seen. Of the 1,600 drugs that have been tested in

TABLE 7–2 FDA Drug Classification System for Pregnancy

Drug Class	Definition
A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.
C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

animals, about one-half cause congenital anomalies; however, there are only 30 documented human teratogens.

4. **Human research** in teratology is generally limited to case series and case-control studies based on registries. Such evidence remains suboptimal and leaves open the potential for erroneous conclusions. For example, many affected pregnancies have other confounding factors, such as other medications as well as the underlying condition being treated. It is often impossible to separate the drug in question from these factors, since finding appropriate matched controls is difficult. Pharmaceutical companies also play a role in the identification of teratogens by participating in postmarketing surveillance studies and running registry programs that aid in the collection of data for pregnancies exposed to these drugs.

5. **Selected teratogenic medications.** Table 7-3 shows some of the more commonly encountered teratogenic drugs and their effects on the developing fetus.

Women taking any of these medications require thorough counseling of the potential risks to an exposed pregnancy, with emphasis of the importance of adequate contraception. Preconception counseling can allow for the woman to be switched to safer medication options prior to attempting conception. In addition, in light of the limitations of teratogenicity research described previously, as well as the individual risk and benefit analysis surrounding a particular scenario, adequate patient counseling cannot be based solely on FDA classification. Rather, such counseling should be based on the available, albeit limited, evidence, as well as a thorough weighing of the risks, benefits, and alternatives for each case. Selected agents with known teratogenic potential will be discussed in further detail as follows.

- a. **Alcohol.** Consumption of alcohol in pregnancy is the most common known teratogenic cause of mental retardation and congenital anomalies. Both miscarriage and stillbirth are increased in heavy drinkers.

TABLE 7-3 Selected Teratogens

Agent	Fetal Effects
ACE inhibitors	Calvarial hypoplasia, renal dysgenesis, oligohydramnios, IUGR, and neonatal renal failure
Alcohol	Syndrome: prenatal and postnatal growth restriction, microcephaly, craniofacial dysmorphism (1-4/1,000 live births); renal, cardiac, and other major malformations increased
Antidepressants (SSRIs)	Cardiac septal defects, neonatal pulmonary hypertension, and neonatal withdrawal syndrome
Carbamazepine	NTDs (1%); possible facial hypoplasia and developmental delay
Corticosteroids	Cleft lip/palate; IUGR increased with high doses
Cyclophosphamide	Craniofacial anomalies, abnormal digits, growth restriction
Isotretinoin	CNS malformations, microtia/anotia, micrognathia, cleft palate, cardiac abnormalities, eye anomalies, limb reduction defects, developmental delay
Lead	Spontaneous abortion, preterm birth and neurodevelopmental delay with maternal serum levels >30 µg/dL
Lithium	Ebstein's anomaly: abnormal tricuspid valve leading to atrialization of the right ventricle
Methotrexate	Syndrome: calvarial hypoplasia, craniofacial abnormalities, limb defects; possible developmental delay
Phenytoin	Microcephaly, facial hypoplasia, hypertelorism, prominent upper lip; growth restriction, developmental delay
Streptomycin	Hearing loss secondary to auditory nerve damage
Tetracycline	Discoloration of teeth and enamel hypoplasia
Tobacco	Possible increase in oral clefts; growth restriction, placental abruption, fetal demise
Valproic acid	Neural tube defects, facial hypoplasia
Warfarin	Fetal warfarin syndrome: nasal hypoplasia, stippled epiphyses, bone hypoplasia, growth restriction; increased risk of demise

- (1) **Fetal alcohol syndrome**, which manifests as mental retardation, growth retardation, abnormal facies, ocular and joint anomalies, and cardiac defects, has been associated with the ingestion of 1 oz or more of absolute alcohol per day. The ‘threshold dose’ of alcohol (the point at which congenital anomalies are induced) is unknown; therefore, no amount of alcohol consumption in pregnancy can be regarded as “safe.”
- (2) **Early exposure**. The critical period for facial dysmorphology has been found to be around the time of conception.
- (3) **Late exposure**. Exposure late in gestation or in small quantities may result in isolated effects, such as learning or behavioral disorders.
- (4) **Heavy alcohol consumption** (more than 3 oz of absolute alcohol or six drinks daily) is associated with some or all of the features of fetal alcohol syndrome, including:
 - (a) **Prenatal or postnatal growth retardation**. Growth retardation is usually prenatal in onset, but postnatal catch-up generally does not occur. It is manifested by decreased birth weight, length, and head circumference.
 - (b) **Central nervous system (CNS) involvement** includes small brain size and brain malformations. Functional deficits, such as moderate mental retardation, delayed motor development, poor coordination, tremulousness, hyperactivity, behavioral disorders and poor attention spans, have been noted.
 - (c) **Characteristic facial dysmorphology** includes a shortened palpebral fissure (observed in more than 90% of affected children); a short, upturned nose; a hypoplastic maxilla; and a thinned upper lip. One study linked craniofacial abnormalities with prenatal alcohol exposure in a dose–response manner.
 - (d) Approximately, 30% of children born to chronic alcoholic women have fetal alcohol syndrome.
- b. **Marijuana**. There is no evidence that smoking marijuana is teratogenic, although the adverse effects of smoking in pregnancy should not be overlooked.
- c. **Heroin** has not been shown to cause structural birth defects, but is associated with severe neonatal withdrawal, leading to death in 3% to 5% of neonates. Methadone is used to treat heroin addiction, and, although it is not teratogenic, it is associated with neonatal withdrawal. Nonetheless, stability on methadone maintenance is associated with much improved outcomes compared to heroin abuse.
- d. **Phencyclidine** (aka “angel dust”) is a hallucinogenic agent that has been associated with facial abnormalities in a small percentage of exposed infants.
- e. **Cocaine** is one of the most abused drugs in pregnancy, second only to alcohol and is associated with an increase in congenital malformations, placental abruption, stillbirths, and low-birth-weight infants. These adverse effects are believed to be related to the drug’s vasoconstrictive properties.
- f. **Cancer chemotherapy**. When cancer chemotherapy is administered during the first trimester of pregnancy, there are varied and unpredictable effects, ranging from severe deformity to no abnormality. The fetal heart, neural tube, and limbs are affected during early organogenesis, with the palate and ears being susceptible later in organogenesis.

After the period of organogenesis (Weeks 2 to 8 postconception), there is less teratogenic risk from chemotherapy in pregnancy, though intrauterine growth restriction, stillbirth, preterm delivery, and low-birth-weight infants are possible with the second- and/or third-trimester exposure. Even after organogenesis, the fetal eyes, genitalia, hematopoietic system, and CNS remain vulnerable to continued exposure.
- g. **Seizure medications**. In general, infants born to epileptic mothers have a **6% to 7% incidence of major and minor congenital abnormalities**. Some studies have suggested that increased seizure frequency leads to higher incidence of malformations and that the malformations may a result of the seizure disorder itself. On the other hand, there is evidence showing an increased risk with higher doses and multiple medications, supporting a more direct link between the seizure medications and anomalies.
 - (1) **Phenytoin** and its derivatives have been associated with **fetal hydantoin syndrome**, which is a constellation of anomalies including growth restriction, microcephaly, facial hypoplasia, hypotelorism, prominent upper lip, and developmental delay. These findings

are generally limited to the first-trimester exposures, although it is best to avoid phenytoin throughout pregnancy if other agents can be effective.

- (2) Valproic acid has been associated with neural tube defects, with a risk as high as 1% to 2% of exposed fetuses.
- (3) Carbamazepine has also been associated with an approximately 1% risk of neural tube defects. In addition, there is some evidence of facial hypoplasia and developmental delay in exposed fetuses as well.
- (4) Recently, newer antiepileptic agents have been gaining more popularity in treating epilepsy patients. The data regarding their use in human pregnancy remain limited. Some data are available which support that lamotrigine may be associated with a lower risk of teratogenicity. The frequency of major birth defects in the registry is 2.9%.

h. Psychotropic drug use in pregnancy. In general, most medications used in the treatment of psychiatric disorders are not known to be associated with a significant risk of teratogenicity.

- (1) One exception is **lithium**, which has been associated with 10- to 20-fold increase in the rate of Ebstein's anomaly after the first-trimester exposure. Fortunately, this remains an exceedingly rare congenital heart defect.
- (2) Selective serotonin reuptake inhibitors (SSRIs) have been associated with a small increase in the risk of cardiac septal defects. In addition, there is some recent evidence linking some SSRIs, such as paroxetine, with persistent pulmonary hypertension in the newborn. Again, the absolute risk remains very small.
- (3) Benzodiazepines are associated with a very small (less than 1%) risk of associated cleft anomalies.

Overall, while patients with psychiatric disorders should be thoroughly counseled about their medications prior to pregnancy, in most cases, the small potential risks are outweighed by the benefits of maintaining good mental health during pregnancy.

i. Warfarin is well-known to have teratogenic potential. Exposure to warfarin during the sixth to ninth weeks of gestation can lead to a constellation of malformations known as **fetal warfarin syndrome** or **warfarin embryopathy**. The characteristics of fetal warfarin syndrome can include:

- (1) Flattened nasal bridge
- (2) Stippled bony epiphyses
- (3) Ocular defects
- (4) Extremity hypoplasia
- (5) Developmental retardation
- (6) Seizures
- (7) Scoliosis
- (8) Deafness/hearing loss
- (9) Congenital heart disease
- (10) Fetal growth restriction
- (11) Death

In addition, warfarin use in pregnancy has been associated with an increased risk of intracranial hemorrhage due to its anticoagulation effects. Thus, warfarin is generally considered contraindicated in pregnancy, especially in the first trimester.

j. ACE inhibitors are commonly used in the treatment of hypertension, especially in diabetic patients. The first-trimester use has been associated with calvarial hypoplasia, renal dysgenesis, and growth restriction. The renal effects on the fetus can be seen even with exposure after the first trimester and can manifest as oligohydramnios and neonatal renal failure.

k. Vitamin A derivatives, such as isotretinoin, have been strongly associated with severe fetal anomalies. Fetuses can present with a variety of anomalies including CNS, eye, ear and thymus anomalies, micrognathia, cleft palate, limb reduction defects, and developmental delay. These malformations are more commonly seen with oral administration in the first trimester. However, even topical retinoids can cause fetal malformations and should be avoided in pregnancy. The concern surrounding vitamin A teratogenicity includes over the counter vitamin supplements. Women in childbearing years should be sure to limit their daily vitamin A intake to less than 8,000 IU.

C Hyperthermia Studies suggest that sustained maternal hyperthermia of more than 102°F (38.9°C) for more than 24 hours between 4 and 14 weeks' gestation is teratogenic. Malformations noted in infants of mothers who were febrile from infectious agents or who frequented saunas in the first trimester include the following:

1. Growth restriction
2. CNS defects, such as mental deficiency, microcephaly, hypotonia, and anencephaly, and increased risk of neural tube defects
3. Facial anomalies, including mid-facial hypoplasia, cleft lip and palate, microphthalmia, micrognathia, and external ear anomalies
4. Minor limb anomalies, such as syndactyly

D Hyperglycemia Infants of insulin-dependent diabetic mothers have up to a 25% incidence of cardiac, renal, gastrointestinal, CNS, and skeletal malformations. Most of the malformations occur between the third- and sixth-week postconception and are increased if there is hyperglycemia during that stage of gestation.

1. The level of risk may be estimated by obtaining glycosylated hemoglobin (hemoglobin A1c) in the first trimester. Levels greater than 8% (depending on the laboratory) have been associated with a 22% increased risk of a fetal anomaly. Strict glucose control preconceptionally has been shown to decrease the frequency of malformations.
2. Two particular **malformations** are found in infants of diabetic mothers:
 - a. **Caudal regression syndrome** with hypoplasia of the caudal spine and lower extremities. This is a very rare syndrome, but when present, is almost pathognomonic for diabetes.
 - b. **Congenital heart disease**, most commonly ventricular septal defects.

E Phenylketonuria (PKU) This genetic disorder is characterized by a deficiency of phenylalanine hydroxylase, a liver enzyme that catalyzes the conversion of phenylalanine to tyrosine. The resulting high levels of phenylalanine in maternal serum result in high levels in the fetus. A special diet low in phenylalanine beginning before conception can prevent the adverse effects (mental retardation) of this disorder. Children born to mothers with PKU who have neglected their special diets are at increased risk for mental retardation, microcephaly, congenital heart disease, and growth restriction.

F Infections Exposure to certain infections during pregnancy has been recognized as a significant cause of birth defects. Knowledge of the potential effects of fetal infection is important for counseling patients with known exposures to these pathogens in pregnancy as well as in the work-up of an abnormal fetus or neonate. In addition, some congenital infections may lend themselves to various interventions to improve outcomes (e.g., fetal transfusion for parvovirus to antibiotics for toxoplasmosis).

1. **Rubella virus (German measles).** When rubella infections occur in the first month of pregnancy, there is a 50% chance of anomalous development. This chance decreases to 22% in the second month and to 6% to 10% in the third to fourth month. The timing of infection is important. If infection occurs during Week 6, cataracts may form. Deafness occurs when infection takes place between Weeks 7 and 8. If a mother is infected at the time of delivery, the newborn may contract pneumonitis or encephalitis.
 - a. **Congenital rubella syndrome** includes the following symptoms:
 - (1) **Neuropathologic changes**
 - (a) Microcephaly
 - (b) Mental and motor retardation
 - (c) Meningoencephalitis
 - (2) **Cardiovascular lesions**
 - (a) Persistent patent ductus arteriosus
 - (b) Pulmonary artery stenosis
 - (c) Atrioventricular septal defects
 - (3) **Ocular defects**
 - (a) Cataracts
 - (b) Microphthalmia

- (c) Retinal changes
- (d) Blindness
- (4) **Inner ear problems**, resulting in sensorineural deafness
- (5) **Symmetric intrauterine growth retardation**
- b. **Rubella vaccination** in childhood is a standard practice. Women of childbearing age found to be nonimmune should receive vaccination. As the rubella vaccine is a live attenuated virus, it should be avoided in pregnancy. However, no sequelae have been reported for incidental rubella vaccination during pregnancy.
- 2. **Cytomegalovirus (CMV)**. This ubiquitous virus infects 1% to 2% of all infants in utero. Between 1 in 5,000 and 20,000 infants suffer severe problems that are recognizable at birth.
 - a. Seronegative mothers infected with primary CMV transmit the infection to the fetus in approximately 40% of cases. Of those infected, 5% to 15% are severely symptomatic at birth with manifestations such as hepatosplenomegaly, jaundice, intracranial calcifications, microcephaly, chorioretinitis, hearing loss, thrombocytopenia, and hepatitis. Of these affected neonates, 30% die and 80% of survivors have severe long-term morbidity. In addition, 10% to 15% of infected infants who are asymptomatic at birth will still develop ocular or auditory sequelae in the first 2 years of life.
 - b. Seropositive mothers who have a recurrent infection transmit the infection to the fetus in only 5% to 10% of cases, and those infants are almost never symptomatic at birth. Nevertheless, there remains the small potential for visual or auditory delays later in childhood.
- 3. **Herpes simplex virus type 2 (HSV-2)**. Although mucocutaneous herpetic infection is common, less than 1 in 7,500 infants suffer from perinatal transmission of HSV-2. Fetal infection can occur during the antenatal course by hematogenous spread during a maternal viremia. Such a congenital varicella infection is exceedingly rare, although several cases have been reported with various sequelae such as cerebral calcifications, microcephaly, microphthalmia, encephalitis, and growth restriction. More commonly, the concern is with neonatal infection via direct contact during passage through an infected birth canal.
- 4. **Toxoplasmosis**, caused by a protozoan, *Toxoplasma gondii*, may be transmitted from mother to fetus antepartum. Although infection is most common outside the United States (e.g., in Sweden), the incidence of congenital infection in the United States ranges from one to six cases per 1,000 live births. Approximately, 30% of infected women transmit the disease to the fetus. Rates of transmission are higher in late pregnancy, but the fetal sequelae are greater when infection occurs in early pregnancy. The disease can be contracted by changing infected cat litter or eating poorly cooked meat. In a population of 550 French women who acquired toxoplasmosis during pregnancy, 61% of the neonates had evidence of congenital infection; of these neonates, 6% died, 5% had severe clinical illness, 9% had mild disease, and 41% had subclinical disease. Fetal infection may result in a spontaneous abortion, perinatal death, severe congenital anomalies, abnormal growth, and residual handicaps. In severe disease, the characteristic triad of anomalies includes chorioretinitis; hydrocephaly or microcephaly; and cerebral calcification, resulting in psychomotor retardation. Treatment of maternal infection with sulfonamides or pyrimethamine (after the first trimester) is indicated. Spiramycin can be used if fetal infection is documented. Treatment during pregnancy and/or in the early neonatal period has been shown to improve outcomes, underscoring the importance of accurate diagnosis.
- 5. **Syphilis** (*Treponema pallidum*). The incidence of syphilis in pregnant women is increasing. The rise in congenital syphilis has paralleled the increase in primary and secondary syphilis in adults. *T. pallidum* appears to be able to cross the placenta at any time during pregnancy. Because the fetus has an immature immune system, it is rarely infected before 16 to 18 weeks' gestation. Before this time, antibiotic therapy is highly successful.

The incidence of congenital infection is inversely proportional to the duration of maternal infection and to the degree of spirochetemia. Recent or secondary infection in the mother confers the greatest risk of fetal infection. All infants born to women with primary and secondary infection are infected, but 50% are asymptomatic. Only 40% of infants born to women with early latent disease are infected, and the incidence drops to 5% to 15% for late latent infection.

In utero infection may result in miscarriage, hydrops, stillbirth, or neonatal death. Congenital infection can manifest as hepatosplenomegaly, characteristic desquamative skin rash, snuffles,

jaundice, pseudoparalysis, anemia, and thrombocytopenia. Later manifestations in childhood include interstitial keratitis, nerve deafness, anterior bowing of (“saber”) shins, frontal bossing, mulberry molars, Hutchinson’s teeth, and saddle nose.

As the tetracyclines are contraindicated in pregnancy and erythromycin may not adequately treat the fetus, pregnant women with syphilis should be treated with IV penicillin G. Penicillin-allergic women should be desensitized to allow for treatment with Penicillin G as it appears to be the most effective in decreasing fetal sequelae.

6. **Varicella zoster virus.** Maternal varicella infection, which can take the form of chickenpox and, later, herpes zoster, occurs in 1 to 7 of 10,000 pregnancies. The infection is much more severe in adults than in children, and pregnancy does not seem to alter this risk. The frequency of fetal infection secondary to the first-trimester maternal infection is less than 5%, although transplacental transmission occurs in about 24% of maternal infections in the last month of pregnancy. Maternal zoster is not associated with a significant risk to the fetus.

Congenital varicella resulting from early fetal infection is rare but can lead to severe manifestations including:

- a. **Cutaneous**

- (1) Cicatricial skin scarring
- (2) Vesicular rash if infection occurs in the last 3 weeks of pregnancy

- b. **Musculoskeletal**

- (1) Limb hypoplasia (unilateral) involving the arm, mandible, or hemithorax
- (2) Rudimentary digits
- (3) Clubfoot

- c. **Neurologic**

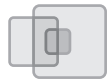
- (1) Microcephaly
- (2) Cortical and cerebellar atrophy
- (3) Seizures
- (4) Psychomotor retardation
- (5) Brain calcifications
- (6) Autonomic dysfunction, such as loss of bowel and bladder control, dysphagia, and Horner syndrome
- (7) Ocular abnormalities, such as microphthalmia, optic atrophy, cataracts, and chorioretinitis

- d. **Other**

- (1) Symmetric intrauterine growth retardation
- (2) Fever, vesicular rash, pneumonia, and widespread necrotic lesions of the viscera, leading to death if infection occurs in the last 3 weeks of pregnancy

In addition to the congenital syndrome, neonatal varicella can occur when maternal viremia occurs around the time of delivery. Thus, neonates born to women with clinical varicella occurring several days prior to and within a few days after delivery should be appropriately treated and monitored.

7. **Mumps.** Mumps infection is not strictly teratogenic; however, after maternal exposure, neonates have been born with endocardial fibroelastosis, ear and eye malformations, or urogenital abnormalities.
8. **Enteroviruses** (Coxsackie B). Serious or fatal illness (40%) in the fetus results from maternal exposure to Coxsackie B virus. Surviving infants may exhibit cardiac malformations; hepatitis, pneumonitis, or pancreatitis; or adrenal necrosis.
9. **Parvovirus B19** infection, otherwise known as erythema infectiosum or “Fifth disease,” can trigger fetal aplastic anemia and lead to congenital heart failure and hydrops fetalis. While the fetal effects are often transient until the fetus clears the infection, the severity of the anemia may lead to the need for in utero fetal transfusion.



Study Questions for Chapter 7

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A 39-year-old G1P0 presents to your office for prenatal care. She denies any significant health problems. She reports being very vigilant about her health and, in addition to a healthy diet and regular exercise, she also takes several vitamin supplements, which she would like to continue taking along with her prenatal vitamin. Excessive intake of which vitamin has been associated with teratogenic potential?

- ☐ A Vitamin D
- ☐ B Vitamin B12
- ☐ C Folic acid
- ☐ D Vitamin A
- ☐ E Vitamin K

2. A 25-year-old woman, G1P0, presents for prenatal care at 8 weeks' gestation with a history of seizure disorder. She reports being well-controlled on lamotrigine, but discontinued it when she found out she was pregnant because of concern for birth defects. However, she reports that since stopping the medication, she has experienced a seizure. She has an appointment with her neurologist in 2 weeks. What is the most appropriate recommendation for this patient?

- ☐ A Start her on valproic acid to protect her from further seizures
- ☐ B Stay off the medication as no antiseizure medication is safe in pregnancy
- ☐ C Defer the decision about medications until she sees her neurologist
- ☐ D Advise her to continue her medication as the benefits of preventing further seizures outweigh the minimal risk of lamotrigine
- ☐ E Advise her to consider termination as the fetus was exposed to her medications during the period of organogenesis

3. A 41-year-old obese woman presents to the emergency room at 25 weeks' gestation with acute shortness of breath. There is concern for pulmonary embolism, and a spiral chest CT scan is recommended. The patient is apprehensive about consenting to the study as she is concerned that the radiation will harm her baby. The most appropriate counseling is to:

- ☐ A Reassure the patient that there is no risk of harm to the fetus from the CT scan
- ☐ B Offer to perform the CT scan with an abdominal shield which will protect the fetus from any radiation exposure
- ☐ C Reassure the patient that while there is indeed some radiation exposure, it is well below the threshold of concern for teratogenicity. Therefore, any potential risks to the fetus are outweighed by the need to rule out a pulmonary embolism
- ☐ D Agree with the patient that the CT scan should be avoided as the fetal radiation exposure approaches 10 rad

4. A 31-year-old woman with diabetes mellitus presents for preconception counseling to discuss the potential impact of her disease on pregnancy. She reports taking pills to manage her diabetes and recently had a hemoglobin A1c of 9.1%. The most appropriate recommendation is to:

- ☐ A Conceive in the near future before her diabetes worsens and puts her at risk of fetal anomalies
- ☐ B Stop her medication prior to attempting to conceive to avoid exposing the pregnancy to medications
- ☐ C Conceive in the near future since her diabetes is optimally controlled
- ☐ D Postpone conception until she can correct her hyperglycemia prior to conception and reduce her risk of fetal anomalies

5. A 38-year-old woman, G4P3, is noted to have significantly elevated blood pressures at 8 weeks' gestation. Given the early gestation age, you explain that she likely has chronic hypertension and recommend that she start an antihypertensive medication. She reports that her sister takes an ACE inhibitor and is very happy with it. You counsel her that:

- ☐ A ACE inhibitors are an excellent choice as it is now after the period of fetal organogenesis
- ☐ B ACE inhibitors are contraindicated, but angiotensin receptor blockers are considered safe in pregnancy
- ☐ C ACE inhibitors are best avoided throughout pregnancy due to potential effects on renal function and amniotic fluid volume
- ☐ D She can start her ACE inhibitor after the first trimester

6. A 20-year-old, G2P0, presents for prenatal care at 12 weeks. Her initial prenatal bloodwork shows that she is nonimmune for rubella. She is concerned with the risks that rubella infection can have on the developing fetus and desires vaccination. You counsel her that:

- ☐ A Congenital rubella is a leading cause of deafness and that vaccination should be administered as soon as possible
- ☐ B Rubella vaccine is a live virus and should be administered only after the first trimester
- ☐ C Rubella vaccine is a live virus and is contraindicated in pregnancy because of the high rate of congenital infection
- ☐ D Rubella vaccination in pregnancy poses a theoretical risk only in pregnancy, but is still contraindicated because of this theoretical risk

QUESTIONS 7–11

Match the fetal anomaly given below with the teratogenic agent most strongly associated with it.

- ☐ A Caudal regression syndrome
- ☐ B Fetal hydantoin syndrome
- ☐ C Neural tube defects
- ☐ D Ebstein's anomaly
- ☐ E Mental retardation

7. Valproic acid

8. Hyperglycemia

9. Alcohol

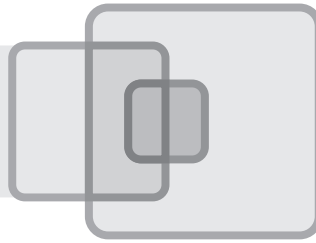
10. Dilantin

11. Lithium



Answers and Explanations

1. **The correct answer is D** [II B 5j]. Intake of vitamin A higher than 8,000 IU daily can be teratogenic to a developing fetus. Women must be made aware of the potential of excessive vitamin A intake with the use of over-the-counter multivitamin and nutritional supplements.
2. **The correct answer is D** [II B 5h]. Several antiseizure medications have been linked to fetal anomalies. Some of the older medications, such as phenytoin and valproic acid, are best avoided in pregnancy, especially during organogenesis. Although there is limited data, it appears that some of the newer agents may be associated with a decreased risk of teratogenicity compared to the older drugs. As it is important to prevent frequent seizures, the patient described should continue her lamotrigine as the risks of additional seizures outweigh the small potential risk of continued lamotrigine use.
3. **The correct answer is C** [II A]. Radiation exposure is a common concern for pregnant women in need of diagnostic imaging. Current guidelines advise avoiding cumulative radiation exposure to the fetus of more than 5 rad. No single diagnostic study reaches that threshold. While abdominal shielding may reduce fetal exposure to some extent, internal scatter still exposes the fetus to radiation. However, given the subthreshold dose and the clinical need to rule out a serious medical complication, the patient should be encouraged to consent to the study.
4. **The correct answer is D** [II D]. Preconception counseling is an effective method to help patients identify modifiable risk factors for pregnancy. Hyperglycemia is strongly associated with several adverse pregnancy outcomes, including an increased risk of fetal malformations. Hemoglobin A1c levels, a marker of glycemic control over the previous 2 to 3 months, is directly related to the risk of fetal anomalies. Patients should be counseled to reduce their hemoglobin A1c levels to less than 6% prior to attempting conception to minimize their risk of a fetal birth defect.
5. **The correct answer is C** [II B 5h]. ACE inhibitors have been associated with renal anomalies and calvarial hypoplasia when used in the first trimester. However, even when used in the second and third trimester of pregnancy, there is concern for potential effects on renal function and amniotic fluid volumes. Thus, the ACE inhibitors should be avoided throughout gestation. While less data are available, given the similarity in mechanism of action, the concern for renal harm also applies to the angiotensin receptor blockers.
6. **The answer is D** [II F 1]. Although the rubella vaccine is a live attenuated virus, there have been no reports of congenital rubella syndrome in pregnancies exposed to the vaccine. Nonetheless, given the theoretical risk of administering live rubella to a pregnant patient, the vaccine is considered contraindicated during pregnancy. Women who were inadvertently vaccinated during pregnancy should be reassured that they are likely at no significant risk. Nonimmune women should be vaccinated postpartum.
- 7–11. **The answers are 7-C** [II B 5h], **8-A** [II D], **9-E** [II B 5a], **10-B** [II B 5h], **11-D** [II B 5i]. These drugs are commonly encountered teratogens. Knowledge of their associations with various anomalies can help in patient counseling and prenatal diagnosis.



Substance Abuse in Pregnancy

VANITA DHARAN JAIN • EILEEN WANG

I

INTRODUCTION

Substance abuse during pregnancy is currently a significant problem in modern obstetrics. It is common to abuse more than one substance at a time.

- A Frequency of occurrence** Use of illicit substances in the general population has become so prevalent that the obstetrician and neonatologist are faced daily with the effects of these drugs on their patients. The true prevalence of drug use in pregnancy is difficult to determine. In the United States, this prevalence, based on urine toxicology, is at a minimum of 10%. The actual number is probably much higher because the urine test is valid for recently used drugs only, and its sensitivity is low.
- B Substances most likely to be abused** Alcohol and cocaine have become the leading abused substances, with alcohol being the most common potentially teratogenic substance in pregnancy. Although other substances are abused in pregnancy, these two substances are examples of how a significant social problem can affect obstetric practice, particularly since pregnancy is often unexpected or unplanned.
- C Problems related to substance abuse** Women who abuse substances while pregnant tend to have other related problems, including sexually transmitted diseases, poor nutrition, and poor prenatal care.

II

DEFINITION

Substance abuse is divided into three stages: use, abuse, and dependence.

- A Use involves** taking low, infrequent doses of illicit substances for experimentation or social reasons. Damaging consequences are rare or minor.
- B Abuse is** the persistent or repeated use of a psychoactive substance for more than 1 month, despite the persistence or recurrence of adverse social, occupational, psychological, or physical effects.
- C Dependence is** present if **three or more of the following criteria** are met continuously for 1 month or repeatedly in a given year:
 1. Abandonment of social, occupational, or recreational activities
 2. Continued substance use despite knowledge of social, psychological, or physical problems exacerbated by drug use
 3. Substance is taken to relieve or avoid withdrawal symptoms
 4. Withdrawal symptoms
 5. Persistent desire or one or more unsuccessful attempts to control substance use
 6. Substance taken in larger amounts or over a longer period than intended
 7. Frequent intoxication or withdrawal symptoms occur when the individual is expected to fulfill obligations at work, school, or home
 8. Significant time spent obtaining or taking the substance or recovering from the effects of its use

III

SIGNS AND SYMPTOMS OF SUBSTANCE ABUSE

- A Screening** All pregnant women should be screened for the use of licit and illicit substances. In addition to positive responses to questioning regarding specific substances, the following clues may alert the physician to an increased risk of substance abuse:
1. Late initiation of prenatal care
 2. Multiple missed prenatal visits or missing work/school
 3. Past obstetrical history significant for unexplained fetal demise, growth restriction, abruption, or precipitous delivery
 4. Children not living with the mother or involved with child protection agencies
 5. Family or partner history of substance abuse
 6. Frequent encounters with law enforcement agencies
- B Physical examination** On physical examination the following may be clues of active substance abuse:
1. Level of arousal: disorientation, euphoria, sedation, agitation, hallucinations, slurred speech, unsteady gait, yawning, papillary dilation, or constriction
 2. Cardiovascular changes: hypertension and tachycardia
 3. Inflamed nasal mucosa, conjunctival injection, particularly track marks—suggest active drug injection
 4. Unusual infections related to drug/alcohol problems: pancreatitis, skin abscesses, subacute bacterial endocarditis, suspicious trauma, hepatitis, and cellulites
- C Laboratory testing** Testing for drug use can be performed on urine, blood, hair, saliva, or sweat. Urine testing is most commonly used because it is easy to obtain and noninvasive. While there are basic toxicology screens, less common illicit/licit drugs may require more specific panels if suspicion for use exists. There is no agreement about the best method for analyzing samples. Because positive tests for illicit drugs can have legal and economic implications, women should give informed consent prior to testing.

IV

PSYCHOACTIVE SUBSTANCES

- A Opiates**
1. **Examples** include heroin, morphine, methadone, and codeine.
 2. **Effects** include euphoria, relaxation, mood elevation, drowsiness, and respiratory depression.
 3. **Associations in pregnancy:** Opiate-dependent pregnant women have been reported to have an increase in obstetrical complications such as preeclampsia, abruption, low birth weight, and perinatal mortality.
 4. **Treatment:** Methadone has been used to treat pregnant opiate addicts for many years. It offers many advantages such as oral administration (vs. injection or inhalation), known dose, purity, and safe/steady availability if obtained from a methadone clinic compared to street drugs. It has not been associated with developmental birth defects. The use of methadone is associated with neonatal abstinence syndrome. The American Academy of Pediatrics considers methadone use compatible with breastfeeding.
- B Depressants**
1. **Examples** include barbiturates, methaqualone, and diazepam (Valium).
 2. **Effects** include euphoria, relaxation, mood elevation, drowsiness, mood volatility, respiratory depression, and impaired coordination.
 3. **Associations in pregnancy:** Methaqualone is a sedative that has been associated with malformations of the eyes, skull, and sternum in animal models. There are no controlled studies on human first-trimester use. There are only isolated case reports of abnormal pregnancy outcome after

recreational use of methaqualone. Benzodiazepines (Diazepam) are not associated with birth defects in human pregnancies. The most important consideration is the risk of neonatal abstinence or withdrawal syndrome, as with all depressive/sedating agents.

C Stimulants other than cocaine

1. **Examples** include amphetamines, especially methamphetamine. Street names include: “crystal meth” and “crank.”
2. **Effects** include euphoria, alertness, sense of well-being, suppression of fatigue and hunger, increased sexual arousal, increased pulse and blood pressure, tremor, insomnia, paranoia, psychosis, and cardiac arrest
3. **Associations in pregnancy:** Definitive information on the impact of in utero exposure is lacking. Most studies focus on prenatal exposure in animal models. The Infant Development, Environment and Lifestyle study included 84 methamphetamine-exposed subjects. The exposed group was 3.5 times more likely to be small for gestational age. Animal data alludes to an increased risk for neurobehavioral alterations in offspring.

D Hallucinogens

1. **Examples** include lysergic acid diethylamide (LSD), mescaline, and psilocybin. Street name includes: “LSD” or “mushrooms.”
2. **Effects** include altered perception, detachment, increased blood pressure, tremor, impaired judgment, and panic.
3. **Associations in pregnancy:** Animal models suggest an increased association with fetal loss. Isolated reports of anomalous infants born to women taking this drug have appeared; however, the evidence is limited.

E Phencyclidine (PCP) and related compounds

1. One **example** is ketamine hydrochloride. Street names include: “angel dust,” “krystal,” and “special K.”
2. **Effects** include detachment, mental numbness, distorted perception, anxiety, and impaired coordination.
3. **Associations in pregnancy:** Animal studies suggest an association with skeletal dysplasias, cleft palate, and microcephaly. School-age children born to mothers who abused PCP during pregnancy have been known to have various mild behavioral and developmental abnormalities.

F Cannabinoids

1. **Examples** include marijuana and hashish. Street names include: “weed,” “hash,” and “grass.”
2. **Effects** include euphoria, relaxation, altered perception, sexual arousal, increased appetite, disorientation, impaired judgment, lack of coordination, and paranoia.
3. **Associations in pregnancy:** Studies have shown that prenatal marijuana use does not appear to increase the risk of birth defects or mortality in the first 2 years of life. However, more recent literature suggests that the area of focus should be in early childhood when exposed infants are exhibiting signs of cognitive deficits, impulsivity, inattention, and hyperactivity.

G Tobacco (nicotine)

1. Twenty-five percent of reproductive-age women are smokers and concurrent use with other substances is a likely possibility. However, smoking is the most important modifiable risk factor associated with adverse pregnancy outcomes.
2. **Effects:** Tachycardia, cardiac dysrhythmia, hypertension, decreased appetite, hypsomnia, vivid dreaming, sleep disturbances, and depression.
3. **Associations in pregnancy:** Increased risk of infertility, miscarriage, abruption, preterm rupture of membranes, stillbirth, preterm delivery, and placenta previa. No increase in congenital anomalies has been seen. Women who smoke are 1.5 to 3.5 times more likely to have a low-birth-weight infant. Interestingly, meta-analysis has shown that maternal cigarette smoking is associated with a reduction in the risk of preeclampsia.

4. **Treatment:** Treatment mostly revolves around behavior modification. Pregnancy provides an opportunity for intervention, and the physician should offer psychosocial intervention and continue to offer it throughout pregnancy. According to the American College of Obstetricians and Gynecologists (ACOG), pharmacotherapy should only be offered if initial counseling fails. Such therapies include nicotine gum, lozenges, patches, or inhalers. Lastly, bupropion (Wellbutrin) has been studied in observational studies among pregnant women and has shown success, where pregnant smokers receiving bupropion were significantly more likely to quit than pregnant controls. However, small studies suggest that there might be an increased risk of congenital anomalies, including congenital heart defects, with the use of this drug in the first trimester.

V

ALCOHOL USE IN PREGNANCY

- A** Alcohol use is the leading cause of teratogenesis by drugs or environmental agents (see Chapter 7). Ethanol crosses the placenta and the fetal blood–brain barrier freely. It is thought to cause toxicity both directly and indirectly by its metabolites.
- B** Women who drink during pregnancy are often older and have higher rates of other illicit drug use, less education, and lower social status.
 1. **Fetal alcohol syndrome** is a congenital syndrome involving a triad of growth retardation, facial abnormalities, and central nervous system (CNS) dysfunction. The **most common abnormalities** are:
 - a. Prenatal and postnatal growth deficiency
 - b. Mental retardation
 - c. Behavioral disturbances
 - d. Atypical facial appearance: short palpebral fissure, epicanthal folds, flat midface, and smooth philtrum with a thin upper lip
 - e. Congenital heart defects
 2. In the United States, the incidence is 1 in 500 to 1,000 deliveries.
- C** **Threshold of alcohol abuse** There is **no safe level of alcohol use in pregnancy**. Patients should be advised that it is safest not to consume any alcohol during pregnancy. The daily consumption of 1 to 2 oz of absolute alcohol (moderate to heavy drinking) may result in infants who show characteristics of fetal alcohol syndrome. Use of smaller amounts of alcohol has also been related to fetal alcohol syndrome. Alcohol is excreted in breast milk. There is evidence that drinking alcohol during breastfeeding may have a detrimental effect on the baby's motor development.
- D** **Alcohol assessment tools** There are three screening tools that have been developed and validated in pregnant women: TWEAK, AUDIT-C, and T-ACE. The T-ACE tool is recommended by ACOG and the National Institute on Alcohol Abuse and Alcoholism for screening all pregnant women for alcohol use and is easily administered.
- E** **Treatment** For women who are alcohol dependent, brief intervention, counseling, and referral to a specialized treatment program are recommended. For nondependent women, a brief in-office intervention may be all that is needed to reduce the risk of an alcohol-exposed pregnancy.

VI

COCAINE USE IN PREGNANCY

The rise in the use of cocaine among the general population has spawned a rise in use among pregnant women, thus making the maternal and fetal complications associated with cocaine use more common. In addition, the increase in rates of exchanging sex for crack cocaine has increased the number of cocaine-complicated pregnancies.

- A** **Use in general population** Cocaine use has increased among the general population because of the availability of inexpensive “**crack**” cocaine, a highly purified form of cocaine that is named for the cracking or popping sound made when the crystals are heated in a test tube. Cocaine can be smoked as crack, taken intranasally, or injected intravenously.

B Pharmacologic effects

1. Cocaine produces **complex cardiovascular effects** that depend on an intact sympathetic nervous system and direct stimulation of the myocardium and vasculature.
2. Cocaine **blocks dopamine and norepinephrine reuptake at the postsynaptic junction**, thereby increasing CNS irritability.
3. This leads to **maternal and fetal vasoconstriction and tachycardia**, as well as **stimulation of uterine contractions**.

C Maternal complications

1. **Neurologic**
 - a. Seizures
 - b. Rupture of intracranial aneurysm
 - c. Postpartum intracerebral hemorrhage
 - d. Cerebral infarction
2. **Cardiovascular**
 - a. Myocardial infarction
 - b. Hypertension
 - c. Arrhythmias
 - d. Rupture of the ascending aorta
 - e. Sudden death
3. **Infectious**
 - a. **Intravenous use** predisposes the patient to bacterial endocarditis, hepatitis, and HIV exposure.
 - b. **Sexually transmitted diseases**, such as gonorrhea, Chlamydia, human papillomavirus, and syphilis, are common, frequently because of the exchange of sex for drugs or sex for money to buy drugs.
4. **Obstetric**
 - a. Possible increase in spontaneous abortions
 - b. Increased incidence of preterm labor and delivery
 - c. Increased incidence of premature rupture of membranes
 - d. Intrauterine growth restriction
 - e. Abruptio placentae (often in conjunction with acute hypertension)
 - f. Increased risk of intrauterine fetal demise
 - g. Increased risk of fetal distress
 - h. Congenital anomalies
 - (1) Fetal microcephaly
 - (2) Nonduodenal intestinal atresia–infarction
 - (3) Limb reduction defects
 - (4) Genitourinary tract anomalies
 - (5) Cerebral infarctions in utero
 - i. Meconium-stained amniotic fluid

D Neonatal complications

1. Decrease birth weight and a dose effect on head size and length
2. Fewer alert periods and less alert responsiveness
3. Cognitive development of children exposed to cocaine in utero is controversial. It can be associated with lower visual–spatial skills, general knowledge, or arithmetic skills

E Management

1. **Detection**
 - a. **Consider drug abuse** in the differential diagnosis.
 - b. **Educate patients** about drug use and its effects on the mother and developing infant.
 - c. **Ask patients directly** about types of psychoactive substances used.
 - d. Examine patients for **inflammation of nasal passages and intravenous injection sites**, especially in patients who do not keep prenatal appointments or who show signs of anemia, fetal growth retardation, or preterm labor.

- e. Consider **urine toxicology screening**. Although this can be used as a method of monitoring and instructing pregnant women about drug use, some states require that these results be reported to government authorities.
 - (1) A **patient–physician alliance** can be best forged through directly confronting a patient about the suspected drug abuse. At that time, the physician can impress on the patient the need to treat the problem in the interest of both herself and the developing infant.
 - (2) **Urine screening** can then be obtained through reasoned persuasion rather than deception.
2. **Treatment**
- a. **Refer the patient to a chemical dependency treatment center.** Ideally, treatment center options should include individual and group counseling, intensive day treatment, and residential treatment. Optimally, residential treatment should include obstetric facilities.
 - b. **Use the assistance of social services** to coordinate a management plan, because a patient's hostile home and social environment (e.g., pervasive poverty, easy access to drugs, or positive opinion of drug culture) can lead to conditions that compound complications caused by cocaine use (e.g., lack of prenatal care and poor nutrition). Dealing effectively with the patient's environment may determine the success or failure of any medical intervention. Involvement of social work may also be necessary to address the issues associated with a positive neonatal toxicology screen and the possible involvement of child protective services.
 - c. **Prevent premature labor and intrauterine growth retardation** using education, nutrition counseling, ultrasound, and fetal testing. Choose magnesium sulfate rather than β -mimetics to treat preterm labor, because magnesium sulfate does not have stimulating effects on the heart muscle.
 - d. With **symptoms of abdominal pain**, differentiate between abruptio placentae, appendicitis, and bowel ischemia. Laboratory evaluation and fetal monitoring clarify the diagnosis and point to the best treatment option (see Chapter 9). Drug screening is essential.
 - e. With **cocaine overdose**, control seizures, hyperthermia, and hypertension by reducing CNS irritability and sympathetic nervous system overactivity. In addition, evaluate the patient's cardiovascular system.
 - (1) Obtain a urine toxicology screen, a complete blood count, and coagulation studies, and measure cardiac and liver enzymes, electrolytes, and arterial blood gas.
 - (2) Administer oxygen and consider intubation for intractable seizures.
 - (3) Monitor urine output, vital signs, and fetal heart rate.
 - (4) Use ice baths or cooling blankets to treat hyperthermia.
 - (5) Treat seizures with magnesium sulfate or diazepam.
 - (6) Maintain normotension and normal heart rate.
 - f. **Consider hospitalization for detoxification**, treatment of psychological disorders, and coordination of further therapy.
 - g. Once **abstinence** has been achieved, perform periodic urine screens to monitor continued abstinence.

VII

SUBSTANCE ABUSE AND PRENATAL CARE

- A** Prenatal care may **reduce the adverse effects of substance abuse** for the mother and fetus.
- B** A **multidisciplinary approach**, including social workers, is essential; substance abusers probably have nonmedical problems that tend to complicate pregnancy.
- C** **Treatment for substance abuse** should be offered.
- D** Intensive **counseling on the risks associated with substance abuse** is essential.
- E** **Laboratory studies, ultrasound examinations, and frequent visits may be necessary** Consider (serial) testing for sexually transmitted diseases if the patient is at high risk for acquisition. Consider obtaining an ultrasound to confirm gestational age, women who use multiple substances are at risk for irregular menstrual cycles or not be very aware of the timing of their cycles, and thus may not be accurately dated. Consider fetal growth evaluation with a third-trimester ultrasound if the illicit substance the patient uses is known to be associated with intrauterine growth restriction.
- F** **Counseling on breastfeeding** and exposure of the infant to substances used by the mother is important. Inform the pediatrician of the possibility of neonatal withdrawal.



Study Questions for Chapter 8

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A 29-year-old female, gravida 1, para 0, presents to your office for her first prenatal visit. While you are reviewing her medical history it is important to ask about which of the following:

- ☐ A Alcohol consumption
- ☐ B Tobacco use
- ☐ C Marijuana use
- ☐ D Cocaine use
- ☐ E All of the above

2. In reference to the patient above, when reviewing her social history she states that she consumes two to three drinks but only when she goes out with her girlfriends after work. Lately she says she has been going out every night, but since her positive pregnancy test 6 weeks ago, she has cut down her consumption to one drink a day. You counsel the patient that there is no safe level of alcohol use in pregnancy, and the safest level is complete abstinence. In addition, you notify her that she is at increased risk for giving birth to a child with:

- ☐ A An omphalocele
- ☐ B Dudodenal atresia
- ☐ C Growth restriction
- ☐ D Low set ears

3. A 40-year-old, gravida 10, para 9, comes into the emergency room complaining of bright red vaginal bleeding. She reports irregular contractions and good fetal movement. She is tachycardic with a heart rate of 120, complaining of chest pain and is short of breath with a blood pressure is 170/100. She is currently at 34 weeks of gestation based on her last menstrual period. She has not obtained prenatal care and states that she does not have time with all her childcare issues. When asked where her nine children are, she states she does not know. Her cervix is 9 cm dilated and 100% effaced. The fetal heart rate tracing is reassuring; however, you notice bright red blood on your glove and on the patient's inner thighs. In addition to sending off laboratory work to evaluate for an acute myocardial infarction, preeclampsia, and renal function, you also send a urine toxicology screen after notifying the patient of your plan. Which substance is most likely to be positive on the drug screen:

- ☐ A Cocaine
- ☐ B Tobacco
- ☐ C Alcohol
- ☐ D Heroin

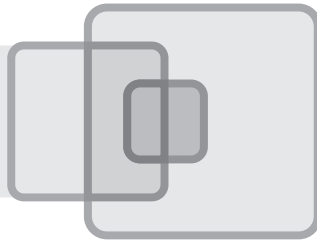
4. A 29-year-old, gravida 2, para 1, at 16 weeks' gestation has a history of smoking three packs of cigarettes a day for the last 15 years. She has made numerous attempts to quit. Her last pregnancy was complicated by fetal growth restriction and preterm delivery at 36 weeks. At her last visit you attempted brief in-office counseling and referred her to an intensive smoking cessation program. Despite her compliance with this program she has been unable to quit. She asks you if there are any medications she can use in pregnancy to help her quit. She does not want to use any nicotine-containing drugs. You offer her:

- ☐ A Prozac
- ☐ B Nicotine gum
- ☐ C Flexeril
- ☐ D Bupropion



Answers and Explanations

1. **The answer is E** [III A]. You must ask about all of the above. Pregnancy is an important time for intervention, but to offer intervention you must find out if your patient needs it. All pregnant women should be screening for both licit and illicit substance abuse at their first prenatal visit.
2. **The answer is C** [V B]. Exposure to alcohol during pregnancy is a preventable cause of birth defects. Rates of fetal alcohol syndrome are on the rise as more women consume alcohol during pregnancy. There is no safe level of alcohol consumption. Fetal alcohol syndrome is characterized by specific facial features (short palpebral fissures, flat upper lip, flattened philtrum, flat midface), evidence of growth restriction, and CNS neurodevelopmental issues.
3. **The answer is A** [VI C]. The third-trimester bleeding is a common complication of pregnancy that threatens both maternal and fetal health. Placental abruption can be caused from preeclampsia, renal disorders, chronic hypertension, multiple gestation, or cocaine use. This patient's history is very suspicious for substance abuse given her agitated behavior, grand-multiparity, and missed prenatal care. In addition, currently she does not know under whose care her children are, suggesting the involvement of child protection services. Cocaine can cause hypertension and acute tachycardia resulting in an acute myocardial infarction. In the management of this patient, two goals should be kept in mind, delivery of the infant and stabilization of the patient's cardiovascular status with blood pressure control.
4. **The answer is A** [IV C H]. Smoking cessation in early pregnancy is very beneficial. Various smoking cessation programs have shown to be effective. Office-based interventions have also been found to be beneficial. However, if women fail to quit smoking after counseling, ACOG guidelines recommend pharmacologic treatment. Since this patient would like to avoid all nicotine-containing substances, your option is bupropion hydrochloride extended-release tablets (Wellbutrin). This drug is considered safe outside of the first trimester; however, the patient should be counseled regarding available literature on the association of this drug and congenital heart defects or other anomalies.



Antepartum Bleeding

DANIELLE BURKLAND

I

INTRODUCTION

Obstetrical hemorrhage remains a direct cause of maternal death in nearly 20% cases. The first-trimester bleeding is associated with spontaneous abortion, ectopic pregnancy, and molar pregnancy (see Chapters 30, 31, and 39). In the third trimester, bleeding is most often associated with placental abnormalities.

II

PLACENTA PREVIA

A Definition Implantation of the placenta over the internal cervical os. There are four degrees of this abnormality:

1. **Total or complete placenta previa.** The placenta completely covers the internal os. Complete previa presents the greatest maternal risk and is associated with the largest amount of blood loss.
2. **Partial previa.** The placenta partially covers the internal os.
3. **Marginal previa.** The edge of the placenta extends to the margin of the internal cervical os.
4. **Low-lying placenta.** The placenta is implanted in the lower uterine segment with the edge of the placenta extends near the internal cervical os.

B Incidence Placenta previa occurs in approximately **1 in 300 live births (0.33%)**. Ultrasound performed in the second trimester may show a placenta previa in 5% to 15% of cases. However, as the lower uterine segment develops, over 90% of these previas will resolve. A repeat ultrasound should be performed at 28 weeks to confirm the presence of a placenta previa.

C Etiology Little is known about the cause of placenta previa. Several epidemiologic risk factors have been identified.

1. Previous placenta previa
2. **Previous cesarean section.** The incidence of placenta previa increases with an increasing number of cesarean sections
3. **Multiparity.** Approximately, 80% of cases of placenta previa occur in multiparous patients
4. **Advanced maternal age**
 - a. Age greater than 35: relative risk of 4.7
 - b. Age greater than 40: relative risk of 9
5. **Smoking.** Increases the risk of placenta previa twofold
6. **Asian and African American** ethnic background
7. **Increasing number of prior curettage (D + C)**

D Clinical presentation **Painless vaginal bleeding** in the third trimester is the most characteristic sign. In cases of placenta previa, a certain amount of spontaneous placental separation is an inevitable consequence of the formation of the lower uterine segment and cervical dilatation. Bleeding may occur in the following circumstances:

1. During rest or activity (70% of bleeding occurs during rest).
2. After trauma, coitus, or pelvic examination. Once the diagnosis of placenta previa is made, patients are instructed to avoid sexual intercourse.

3. During labor, when the lower uterine segment begins to efface and dilate. The tearing of the placental attachments at or near the internal cervical os causes the bleeding.

E Diagnosis Placenta previa should be considered in all patients who present with vaginal bleeding after 20 weeks. Women suspected of having a placenta previa should undergo an **ultrasound** to determine the position of the placenta. Digital and pelvic examination is deferred until the diagnosis of placenta previa is excluded by ultrasound.

1. **Ultrasound. Transabdominal ultrasound is a safe and precise with an accuracy of greater than 95%.** Transvaginal ultrasound may also be performed when the diagnosis is still in question which improves the diagnostic accuracy of ultrasound.
2. **Double set-up examination.** Prior to the availability of ultrasound nearly 24 hours a day, cervical examination was performed. Definitive diagnosis of placenta previa can be made by clinical palpation of placenta tissue through the cervical os and should only be attempted during a **double set-up** examination (i.e., the patient is in the delivery room prepared for a vaginal examination and an emergent cesarean section), as it may precipitate a hemorrhage. Therefore, it is performed only when:
 - a. Delivery is contemplated at the time of the examination.
 - b. The examination is performed in the operating room with the patient prepped for surgery, an anesthesiologist present, the surgeon scrubbed, and blood cross-matched and available.
 - c. The pregnancy is at or near term.

F Management Treatment depends on gestational age, amount of vaginal bleeding, maternal hemodynamic status, and fetal condition.

1. **Expectant management.** This approach is justifiable if the fetus is preterm (less than 37 weeks) and can benefit from further intrauterine development. Expectant management should proceed as follows:
 - a. Hospitalization until bleeding subsides. The patient may be discharged after the bleeding resolves.
 - b. Continuous electronic fetal monitoring during initial evaluation.
 - c. Steroids for fetal lung maturity if gestational age is less than 34 weeks.
 - d. Tocolysis (see Chapter 15) may be safely undertaken in patients with placenta previa before 34 weeks. The agent of choice is magnesium sulfate because it is associated with fewer hemodynamic alterations.
2. **Delivery.** Decisions concerning delivery are made on the basis of the gestational age of the fetus, the amount of vaginal bleeding, and maternal hemodynamic status. Indications for **cesarean section** include:
 - a. **Elective**
 - (1) When the gestational age is **37 weeks**
 - (2) When **fetal lung maturity** is demonstrated by amniocentesis
 - b. **Emergent**
 - (1) When the amount of bleeding presents a threat to the mother or fetus regardless of gestational age or fetal size.
 - (2) Nonreassuring fetal heart rate tracing.

G Maternal and fetal complications Maternal and fetal morbidity can occur from a pregnancy with placenta previa and may be significant.

1. **Maternal morbidity**
 - a. **Maternal hemodynamic shock** can result from acute blood loss.
 - b. **Severe postpartum hemorrhage (PPH)** can occur after the delivery because the placental implantation is in the lower uterine segment, which has decreased muscle content. Thus, muscle contraction may be less effective in controlling the bleeding. PPH may lead to the following conditions:
 - (1) **Renal damage** (acute tubular necrosis), which may result from prolonged hypotension
 - (2) **Pituitary necrosis (Sheehan syndrome)** and resulting panhypopituitarism
 - (3) **Disseminated intravascular coagulation (DIC)** due to excessive blood loss and possible death

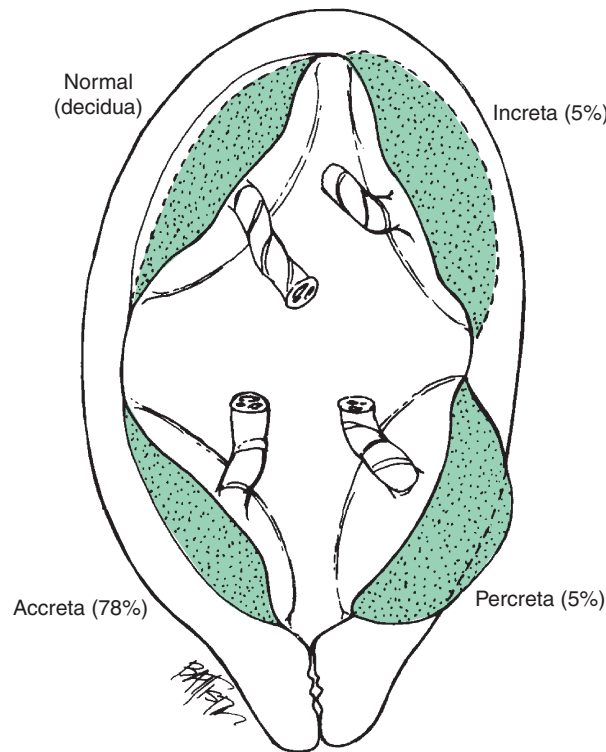


FIGURE 9–1 Uteroplacental relationships found in abnormal placentation. (From Niebyl JR, Simpson JL, Gabbe SG. *Obstetrics: Normal and Problem Pregnancies*. 4th Ed. London: Churchill Livingstone, 2001).

- c. **Placenta accreta** (growth of placenta into the myometrium), or any of its variations, due to the absence of decidua basalis. Placenta accreta should always be considered in the presence of placenta previa.
 - (1) The incidence of placenta accreta in the setting of placenta previa is 1% to 5% in an unscarred uterus. The incidence of placenta accreta increases to 11% to 25% after a previous cesarean section. The incidence of placenta accreta increases to more than 50% after four previous cesarean sections.
 - (2) The presence of a placenta accreta may necessitate a cesarean hysterectomy to control the blood loss. There are three types of placenta accreta (Fig. 9–1):
 - (a) **Placenta accreta.** The placenta is abnormally attached directly to the myometrium.
 - (b) **Placenta increta.** The placenta invades the myometrium.
 - (c) **Placenta percreta.** The placenta penetrates completely through the myometrium.
2. **Fetal morbidity. Preterm delivery** may be necessary secondary to maternal bleeding.
 - a. Neonatal mortality rate is three times higher in pregnancies complicated by previa due to increased preterm delivery.

III

ABRUPTIO PLACENTAE (PLACENTAL ABRUPTION)

A Definition Abruptio placenta is a premature separation of a normally implanted placenta.

1. **Pathophysiology.** Initiated by bleeding into the decidua basalis, the bleeding splits the decidua, and a decidual hematoma forms. The hematoma leads to separation, compression, and destruction of the placenta adjacent to it.
 - a. The process may be **self-limited**, with no further complication to the pregnancy or may continue to become catastrophic.
 - b. Bleeding insinuates between the fetal membranes and uterus which may extravasate or may remain concealed. Concealed abruptions can often be more compromising to maternal hemodynamic status since they are generally underappreciated.

B Incidence

1. The reported incidence of abruptio placentae is about **1 in 200 births**.
 - a. Abruptio severe enough to kill the fetus occurs in **1 in 1,600 births**.
 - b. Abruptio is identified as a cause in up to 10% to 15% of all stillbirths.

C Etiology The primary cause of abruptio placentae is uncertain; several associated conditions have been identified. Incidence increases with maternal age. Abruptio was more common in African American and Caucasian women compared with Asian and Latin American women.

1. **Maternal hypertension**, chronic, gestational, or preeclampsia, is the most often identified risk factor and is associated with a three- to fourfold increase.
2. **Cocaine** use is associated with both an increase in maternal hypertension and vasoconstriction of the placental vasculature. Recent increases in cocaine use have led to an increase in the number of cases of abruptio placentae.
3. **Preterm premature rupture of membranes (PPROM)** has been associated with cases of abruptio placentae. The incidence of abruptio placentae is 5% in pregnancies between 20 and 36 weeks complicated by PPRM.
4. **Maternal trauma** accounts for a small number of cases of abruptio placentae. Clinical evidence of abruptio is not always immediately apparent. A period of prolonged monitoring is required to exclude developing abruptio placentae.
5. Either **sudden decompression** of the uterus by rupture of membranes in a patient with polyhydramnios, or delivery of a first twin, can lead to a shearing effect on the placenta as the uterus contracts, thus causing abruptio placentae.
6. **Cigarette smoking** is associated with decidual necrosis on pathologic examination and an increased risk of abruptio placentae. This risk is increased in patients with chronic hypertension as well.
7. **Uterine fibroids** may contribute to abruptio placentae when the placenta is implanted directly over the fibroid.
8. **History of abruptio placentae** predisposes patients to subsequent abruptios; the risk is increased tenfold (0.4% to 4%). Placental abruptio is frequently a sudden event and not predicted with antenatal testing.
9. **Thrombophilia**: both inherited, such as Factor V Leiden and acquired, such as antiphospholipid antibody syndrome.

D Clinical presentation The clinical signs of abruptio including vaginal bleeding, abdominal pain, and uterine contractions. The severity of the clinical presentation is variable:

1. Partial placental abruptio in which no maternal or fetal compromise is noted.
2. Complete placental abruptio with profuse bleeding, signs of maternal DIC, and a stillbirth.

E Diagnosis The basis of diagnosis consists of history, clinical examination, and a high index of suspicion. The **triad of vaginal bleeding, uterine or back pain, and fetal distress is common**.

1. **Fetal heart rate monitoring** may reveal loss of variability or may have late decelerations. The uterine tone may be increased without periods of relaxation.
2. **Premature contractions** that are unresponsive to tocolytics may suggest either abruptio placentae or intra-amniotic infection.
3. **Ultrasound** confirmation occurs only in 25% of cases. A retroplacental clot may not be detected unless a very large abruptio occurs.
4. **Laboratory tests** are nonspecific but may reveal thrombocytopenia, hypofibrinogenemia, and anemia. Remember a normal fibrinogen level in a pregnant woman is higher than normal, around 400 mg/dL.

F Management Treatment depends on the condition of the mother, the fetus, and the gestational age of the fetus.

1. **Maternal hospitalization** with continuous fetal monitoring and close surveillance of maternal status.
 - a. **Delivery may be delayed in the preterm fetus** if the fetal heart rate tracing is reassuring and the maternal condition remains stable.
 - b. **Immediate cesarean delivery is necessary** in the following conditions:
 - (1) Fetal heart rate tracing is nonreassuring
 - (2) Maternal hemodynamic instability
 - c. **Vaginal delivery is desirable** if the maternal and fetal condition permits.
2. The use of **tocolytic drugs** (see Chapter 15) is controversial in the setting of placenta abruption in a pregnancy less than 34 weeks. If tocolysis is to be considered, maternal and fetal status must be reassuring.
 - a. **Magnesium sulfate** is the tocolytic of choice because of its efficacy and side effect profile.
 - b. β -mimetic tocolytics should be avoided in cases of suspected abruptio placentae because they may mask maternal hypovolemia by causing tachycardia.
 - c. **Prostaglandin inhibitors** should be used with caution because they are associated with a theoretic risk of platelet dysfunction.
3. **Complications**
 - a. **Hemorrhagic shock** may occur either from external bleeding or from concealed clots. Treatment includes:
 - (1) Aggressive intravenous fluid replacement
 - (2) Replacement of blood loss and coagulation factors
 - (3) Prompt delivery after maternal stabilization
 - b. **Consumptive coagulopathy (DIC)** may occur in 30% of cases of severe abruptio placentae that lead to fetal demise.
 - c. **Renal failure**, in the form of acute tubular necrosis, may result from intrarenal vasospasm or from massive hemorrhage and ensuing hypotension.
 - d. **Couvelaire uterus** results from extravasation of blood into the myometrium. The hematoma seldom interferes with uterine contractions, and the uterus responds well to uterotonic agents. A Couvelaire uterus is not an indication for hysterectomy.
 - e. **Fetal maternal hemorrhage** or the presence of fetal red blood cells in the maternal circulation is more commonly seen with traumatic instances of abruptio placentae. Rh-negative patients should receive RhoGAM (anti-D immune globulin).

IV

OTHER CAUSES OF THE THIRD-TRIMESTER BLEEDING

A Obstetric causes

1. **Bloody show** is a normal part of labor, bleeding is usually minimal, and the blood is mixed with mucus.
2. **Vasa previa** is a rare but very serious cause of vaginal bleeding. The bleeding is fetal in origin.
 - a. Vasa previa is a condition associated with velamentous cord insertion where fetal vessels in the membranes cross the region of the cervical os. Membrane rupture can be accompanied by tearing of fetal vessel with exsanguination of the fetus.
 - b. Vasa previa is usually detected antenatally during the level II ultrasound.
3. A **uterine rupture** must be considered if a patient has a history of previous uterine surgery.

B Nonobstetric causes

1. **Vaginal lacerations from trauma**
2. **Vaginal infections**, such as candida or trichomonas
3. **Cervical pathology**, such as gonorrhea, Chlamydia, cervical polyps, or cervical cancer



Study Questions for Chapter 9

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A 39-year-old woman, gravida 2, para 1, at 36 and 4/7th weeks of gestation with a history of prior cesarean section in the setting of placental abruption presents with abdominal pain and vaginal bleeding. She admits to using cocaine. Her vital signs are significant for T = 99.9, HR = 120, BP = 170/100. Fetal heart rate baseline is in the 160s with minimal variability and repetitive late decelerations. Her bloodwork is significant for a hemoglobin of 7.5, platelets of 110,000, and a fibrinogen level of 250 mg/dL. All of the following are risk factors for this patient's condition except:

- ☐ A Advanced maternal age
- ☐ B Cocaine
- ☐ C Prior cesarean section
- ☐ D Hypertension
- ☐ E Prior placental abruption

2. A 33-year-old woman, gravida 7, para 3214, presents at 28 weeks with complaints of vaginal bleeding. She denies abdominal or back pain. She has had no prenatal care. She reports recent intercourse. On presentation, she has light vaginal bleeding and fetal heart tones are reassuring. The most useful next step in her evaluation would be:

- ☐ A Digital examination
- ☐ B Complete blood count (CBC), coagulation profile
- ☐ C Ultrasound
- ☐ D Immediate cesarean delivery
- ☐ E A double set-up examination

3. A 20-year-old woman, gravida 1, para 0, at 33 weeks of gestation arrives to labor and delivery reporting profuse vaginal bleeding and abdominal pain. Her vitals are as follows: T = 96.8, BP = 78/40, P = 138, R = 28. Her abdomen is firm and tender to touch. Fetal heart tones are in the 160s with minimal variability and late decelerations. Tocometer demonstrates contractions every 1 to 2 minutes. Ultrasound demonstrates a cephalic fetus, placenta is fundal and free of the os without a retroplacental clot. Cervical examination is 3/90/–1. Which is the most appropriate management plan?

- ☐ A Betamethasone and magnesium for tocolysis with maternal transfusion as needed
- ☐ B Augmentation of labor with amniotomy and pitocin
- ☐ C Immediate cesarean delivery with appropriate maternal and fetal resuscitation
- ☐ D Betamethasone and indocin for tocolysis
- ☐ E Intravenous fluid resuscitation and ephedrine

4. A 34-year-old woman, gravida 5, para 4004, at 30 and 2/7th weeks of gestation presents to labor and delivery reporting vaginal bleeding. She reports vague back pain. Her blood pressure is 110/78 and her pulse is 106. She has slow, continuous bleeding from her vagina. Her cervix appears long and closed on speculum examination. Fetal monitoring reveals one uterine contraction every 30 minutes, and the fetal heart rate is reassuring. Transabdominal ultrasound demonstrates a complete placenta previa. The most appropriate next step would be:

- ☐ A Magnesium sulfate
- ☐ B Cesarean delivery
- ☐ C Oxytocin
- ☐ D Discharge home on bed rest
- ☐ E Betamethasone

5. A 32-year-old woman, gravida 5, para 2022, at 36 weeks of gestation with placenta previa presents to labor and delivery with vaginal bleeding. After evaluation, decision to proceed with a cesarean delivery was made. She has a history of two previous low transverse cesarean sections. Delivery by low transverse cesarean section is complicated by placenta accreta. Estimated blood loss was 3.7 L. The patient is at risk for all of the following except:

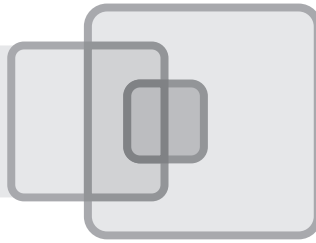
- ☐ A Consumptive coagulopathy
- ☐ B Sheehan syndrome
- ☐ C Acute tubular necrosis
- ☐ D Couvelaire uterus
- ☐ E Emergent hysterectomy



Answers and Explanations

1. **The answer is C.** The patient is experiencing a placental abruption. Her risk factors for placental abruption include a prior history of placental abruption, advanced maternal age, cocaine use, and hypertension. Prior cesarean delivery is not associated with increased risk of placental abruption.
2. **The answer is C.** This patient presents with painless vaginal bleeding after intercourse, with no previous ultrasound performed and likely has bleeding from an undiagnosed placenta previa. A transabdominal ultrasound will be the most useful test to confirm this diagnosis. A digital examination would be contraindicated until placental localization was determined. Double set-up examination does not need to be performed in most circumstances due to availability of ultrasound; especially in this case of a preterm fetus in which both maternal and fetal status is reassuring. Labwork will not confirm the diagnosis and cesarean delivery is not necessary at this time.
3. **The answer is C.** The clinical scenario is most indicative of a placental abruption with maternal hemodynamic instability and fetal status is not reassuring. This warrants immediate and expeditious delivery by cesarean. Although the fetus is preterm and would receive benefit from steroids, given the maternal and fetal instability, there is no time to administer steroids and await their benefit.
4. **The answer is E.** This clinical scenario is consistent with an initial bleed in the setting of placenta previa. Expectant management is justifiable if the fetus is preterm (less than 37 weeks) and can benefit from further intrauterine development. Betamethasone is indicated given the risk of preterm delivery in patients with placenta previa complicated by vaginal bleeding. Hospitalization is appropriate until the bleeding subsides. The patient may be discharged after the bleeding lessens and the physician judges that the fetus is healthy. Tocolysis (magnesium sulfate) is not necessary because the patient is not having significant, regular uterine contractions and the cervix appears closed. Vaginal delivery or cesarean section is not necessary at this point because the pregnancy is preterm, the mother's vital signs are stable, and the fetus is stable (reactive on fetal monitoring strip).
5. **The answer is D.** A patient with placenta accreta will need a hysterectomy in most circumstances. The large blood loss will place the patient at risk for consumptive coagulopathy, acute tubular necrosis, and Sheehan syndrome if blood product replacement is not performed in a timely manner. Couvelaire uterus finding is noted in the setting of placenta abruption when blood has extravasated into the myometrium.

chapter 10



Labor and Delivery

YU-HSIN WU

I

THEORIES OF THE CAUSES OF LABOR

The exact mechanism by which labor is initiated spontaneously, at either term or preterm, is not known. Many theories have been proposed.

A Oxytocin stimulation Endogenously produced oxytocin, which causes uterine contractions, may play a role in the spontaneous onset of labor.

1. Levels of oxytocin in maternal blood in early labor are higher than before the onset of labor, but there is no evidence of a sudden surge.
2. Oxytocin influence must therefore rely on the presence of oxytocin receptors.
 - a. Receptors are found in the nonpregnant uterus.
 - b. There is a sixfold increase in receptors at 13 to 17 weeks' gestation and an 80-fold increase at term.
 - c. The increased number of oxytocin receptors amplifies the biologic effect of oxytocin, and contractions intensify.

B Fetal cortisol levels Fetal cortisol levels may influence the spontaneous onset of labor.

1. Disruption of hypothalamic–pituitary–adrenal axis or the absence of adrenal gland or function results in prolonged gestation in humans and sheep. In sheep, infusion of cortisol or ACTH into a fetus with an intact adrenal gland causes premature labor.
2. However, in humans, there has been no documentation of prelabor surge in fetal cortisol secretion to completely support this theory.

C Progesterone withdrawal

1. In rabbits, the withdrawal of progesterone is followed by the prompt evacuation of the contents of the pregnant uterus.
2. In humans, there is no obvious decrease in maternal blood levels of progesterone at term or in labor. However, the progesterone level at the placental site may decrease before the onset of labor. This decrease in progesterone, in association with increased estrogen levels, is followed by increased formation of gap junctions, which permit coupling of the myometrial cells.

D Prostaglandin release Prostaglandins, particularly $\text{PGF}_{2(\alpha)}$ and PGE_2 , have long been believed to be involved in the spontaneous onset of labor. The normal processes of labor appear to result in inflammation, which results in increased prostaglandin synthesis. Prostaglandins produced in myometrial tissue may contribute to the effectiveness of myometrial contractions during labor, and may soften the cervix independent of uterine activity.

II

DEFINITION AND CHARACTERISTICS OF LABOR

A Definition Labor is regular, painful contractions that result in progressive cervical dilation and effacement.

B Stages of labor

1. *First stage (cervical stage).* The first stage of labor entails cervical change. It begins when uterine contractions become sufficiently strong or adequate to initiate effacement and dilation of the cervix.

- a. *Effacement* of the cervix is the shortening of the cervical canal into a paper-thin orifice. Effacement occurs as the muscle fibers near the internal os are pulled upward into the lower uterine segment.
 - b. *Dilation* of the cervix involves the gradual widening of the cervical os. For the head of the average fetus at term to be able to pass through the cervix, the cervix must dilate to a diameter of approximately 10 cm. When the fetal head is able to descend past the remaining cervix, the cervix is no longer palpable and is said to be completely or fully dilated.
2. *Second stage (pelvic stage)*. The second stage of labor involves the passage of the fetus through the maternal pelvis and expulsion of the fetus. It begins with the complete dilation of the cervix and ends when the infant is delivered. According to the Friedman curve:
 - a. In a nulliparous patient, the second stage of labor should last less than 2 hours without regional anesthesia, and less than 3 hours if a woman has regional anesthesia.
 - b. In a multiparous patient, the second stage of labor should last less than 1 hour without regional anesthesia, and less than 2 hours if a woman has regional anesthesia.
 3. *Third stage (placental stage)*. The third stage of labor involves the separation and expulsion of the placenta. It begins with the delivery of the infant and ends with the delivery of the placenta.

C Components of labor (the three P's)

1. *Powers* = Contractions
 - a. As uterine contractions involve increasing numbers of myometrial fibers, the intensity and duration of the contractions increase. In early labor, the contractions occur every 5 to 10 minutes, last for 30 to 45 seconds, and are 20 to 30 mm Hg in intensity. As labor progresses, the contractions occur every 2 to 3 minutes, last for 50 to 70 seconds with 40 to 60 mm Hg in pressure/intensity.
 - b. The myometrial fibers of the upper portion of the uterus shorten, and therefore the wall of the upper uterus thickens. As a result of labor the lower uterine segment thins out, the cervix is “taken up” into this segment, and is eventually pulled over the fetal presenting part. At this time, a woman is considered to be fully/completely dilated.
2. *Passenger* = The fetus
 - a. *Presentation*—indicates that portion of the fetus that overlies the pelvic inlet, and can be determined by inspection and palpation of the maternal abdomen (Leopold's maneuvers).
 - (1) Cephalic—occurs in approximately 95% of at or near-term labors. The type of cephalic presentation depends on the degree of flexion or extension of the fetal head.
 - (a) Vertex—head is well flexed and the parietal bones are presenting.
 - (b) Face—head is completely extended and face is presenting.
 - (c) Brow—head is deflexed (or only partially extended), the brow is presenting and cannot deliver vaginally because the largest anteroposterior diameter of the head is trying to negotiate through the maternal pelvis.
 - (2) Breech—occurs in approximately 3.5% of at or near-term labors.
 - (a) Frank breech—thighs flexed, legs extended over anterior aspect of abdomen
 - (b) Complete breech—thighs flexed, legs flexed
 - (c) Incomplete or footling breech—knees and feet, one or both, are lowest and presenting
 - (3) Shoulder—0.4% of at or near-term labors
 - (4) Face—0.3% of at or near-term labors
 - b. *Position*—the relation of the fetal presenting part to the maternal pelvis.
 - (1) Markers for position are:
 - (a) Occiput for vertex presentation
 - (b) Sacrum for breech presentation
 - (c) Mentum (chin) for face presentation
 - (d) Acromion for shoulder presentation
 - (2) The designated fetal bony point is related to the maternal pelvis:
 - (a) Right or left
 - (b) Anterior, posterior, or transverse

3. *Passage* = The pelvis

- a. *Gynecoid*—most common and best suited for childbearing. A wide pubic arch, straight sidewalls, curved sacrum and not prominent ischial spines, facilitate passage of a fetus.
- b. *Android*—not favorable for delivery. The pubic arch is narrow, the sidewalls are convergent, the sacrum is anteriorly inclined, and the ischial spines are prominent, all of which are more obstructive to fetal passage.
- c. *Anthropoid*—diameter is long from front to back and relatively narrow from side to side.
- d. *Platypelloid*—least common type. Wide transverse dimensions but shortened anteroposterior dimensions.

III

NORMAL LABOR IN THE OCCIPUT PRESENTATION

A Occiput (vertex) presentations By palpating for the anterior and posterior fontanelles, the position of the occiput can be determined. The occiput may present in transverse, anterior, or posterior and right or left position (Fig. 10–1).

1. Occiput transverse (OT)—The sagittal suture (suture from front to back, in the midline) of the fetal head occupies the transverse diameter of the pelvis more or less midway between the sacrum and the symphysis.

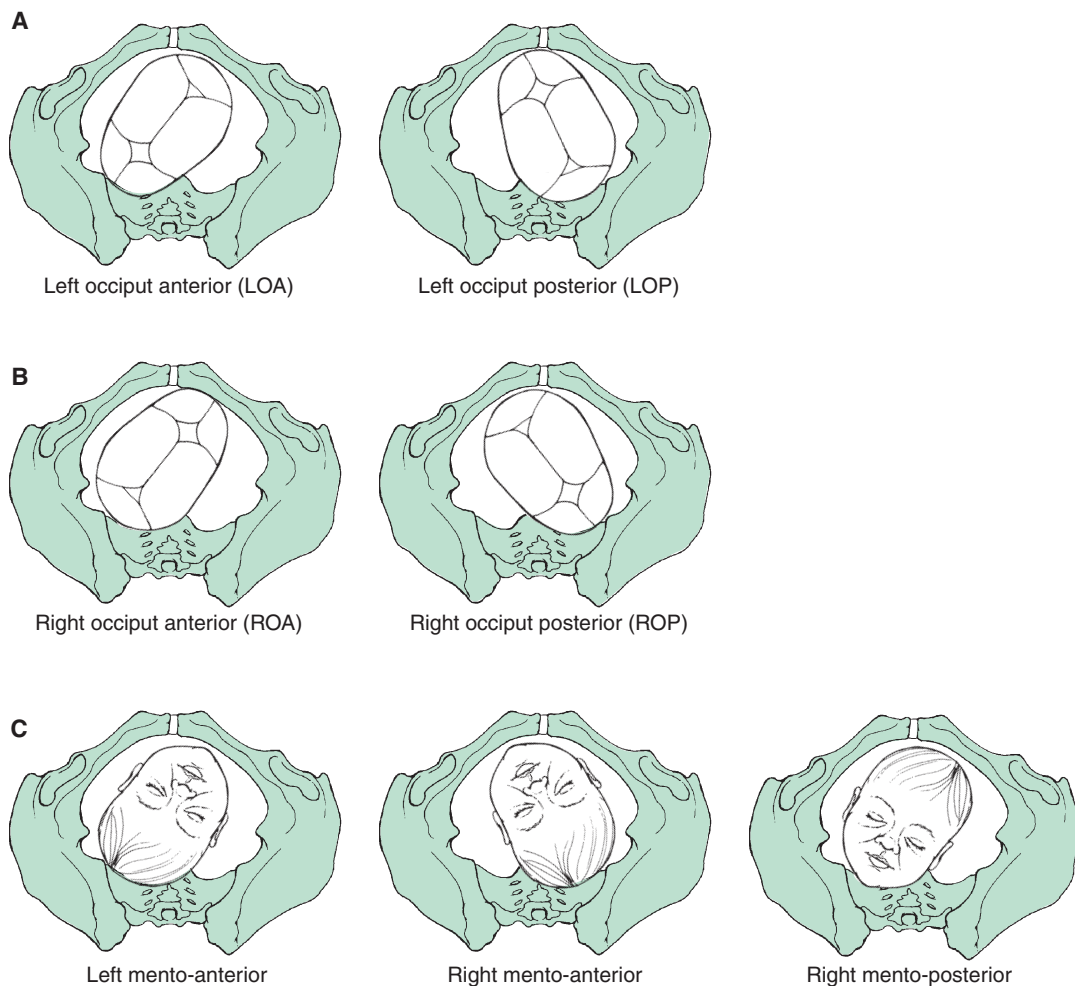


FIGURE 10–1 Occiput and face presentations in labor. (From Pritchard JA, MacDonald PC, Gant NF. Williams Obstetrics. 21st Ed. New York: McGraw-Hill, 2001:294–296).

- a. In the left occiput transverse positions (LOT), the smaller posterior fontanelle (triangle shaped with three sutures radiating from it) is on the left side of the maternal pelvis, and the larger anterior fontanelle (diamond shaped with four sutures radiating from it) is on the opposite right side of the maternal pelvis.
 - b. In the right occiput transverse positions (ROT), the reverse is true.
2. Occiput anterior (OA)—The head enters the pelvis with the occiput anteriorly, and rotated away from the transverse position.
 - a. Direct occiput anterior (DOA)—posterior fontanelle in midline, under pubic symphysis
 - b. Right occiput anterior (ROA)—posterior fontanelle is between DOA and ROT
 - c. Left occiput anterior (LOA)—posterior fontanelle is between DOA and LOT
3. Occiput posterior, aka “sunny side up,” where the fetus is facing up at delivery. The posterior positions are often associated with a narrow forepelvis.
 - a. Direct occiput posterior (DOP)—posterior fontanelle is midline and posterior, closer to sacrum
 - b. Right occiput posterior (ROP)—posterior fontanelle is between DOP and ROT
 - c. Left occiput posterior (LOP)—posterior fontanelle is between DOP and LOT

B **Second stage of labor** and mechanism of labor and delivery involve seven cardinal movements. A process of positional adaptation of the fetal head to the various segments of the pelvis is required to complete childbirth. These positional changes occur sequentially in the following order: engagement, descent, flexion, internal rotation, extension, external rotation, and expulsion (Fig. 10–2).

1. *Engagement.* The biparietal diameter of the fetal head, the greatest transverse diameter of the head in occiput presentations, passes through the pelvic inlet.
 - a. When engagement occurs, the lowest point of the presenting part is, by definition, at the level of the ischial spines, which is designated as 0 station. Levels 1, 2, and 3 cm above the spines are designated as –1, –2, and –3 stations, respectively; levels 1, 2, and 3 cm below the spines are designated as +1, +2, and +3 stations, respectively. At +3, the presenting part is on the perineum.
 - b. Engagement may take place during the last few weeks of pregnancy, or it may not occur until labor begins. It is more likely to happen before the onset of labor in a primigravida. In multigravid women, the fetal head is less likely to be engaged at the onset of labor, and the fetal head is floating or freely movable above the pelvic inlet.
2. *Descent.* The first requirement for the birth of an infant is descent. In primigravidas, while engagement may take place before the onset of labor, further descent may not follow until the onset of the second stage. In multiparous women, descent usually begins with engagement.
3. *Flexion.* When the descending head meets resistance from either soft or bony tissue in the pelvis, flexion of the fetal head normally occurs.
 - a. The chin is brought into close contact with the fetal thorax.
 - b. This movement causes a smaller diameter of fetal head (biparietal diameter) to be presented to the pelvis, instead of the longer occipitofrontal diameters.
4. *Internal rotation.* It occurs at the level of the ischial spines (0 station). This movement involves the gradual turning of the occiput anteriorly, such that the sagittal suture runs anteroposteriorly as the fetal vertex descends through the plane of the midpelvis.
5. *Extension of the fetal head.* This extension is essential during the birth process. When the sharply flexed fetal head meets the vulva, the occiput is brought in direct contact with the inferior margin of the symphysis.
 - a. Because the vulvar outlet is directed upward and forward, extension must occur for the head to pass through.
 - b. The expulsive forces of the uterine contractions and the woman’s pushing, along with resistance of the pelvic floor, result in the anterior extension of the vertex in the direction of the vulvar opening.
6. *External rotation.* After delivery of the head, restitution occurs. In this movement, the occiput returns to the oblique position from which it started and then to the transverse position, left or right. This movement corresponds to the rotation of the fetal body, bringing the shoulders into an anteroposterior diameter with the pelvic outlet.

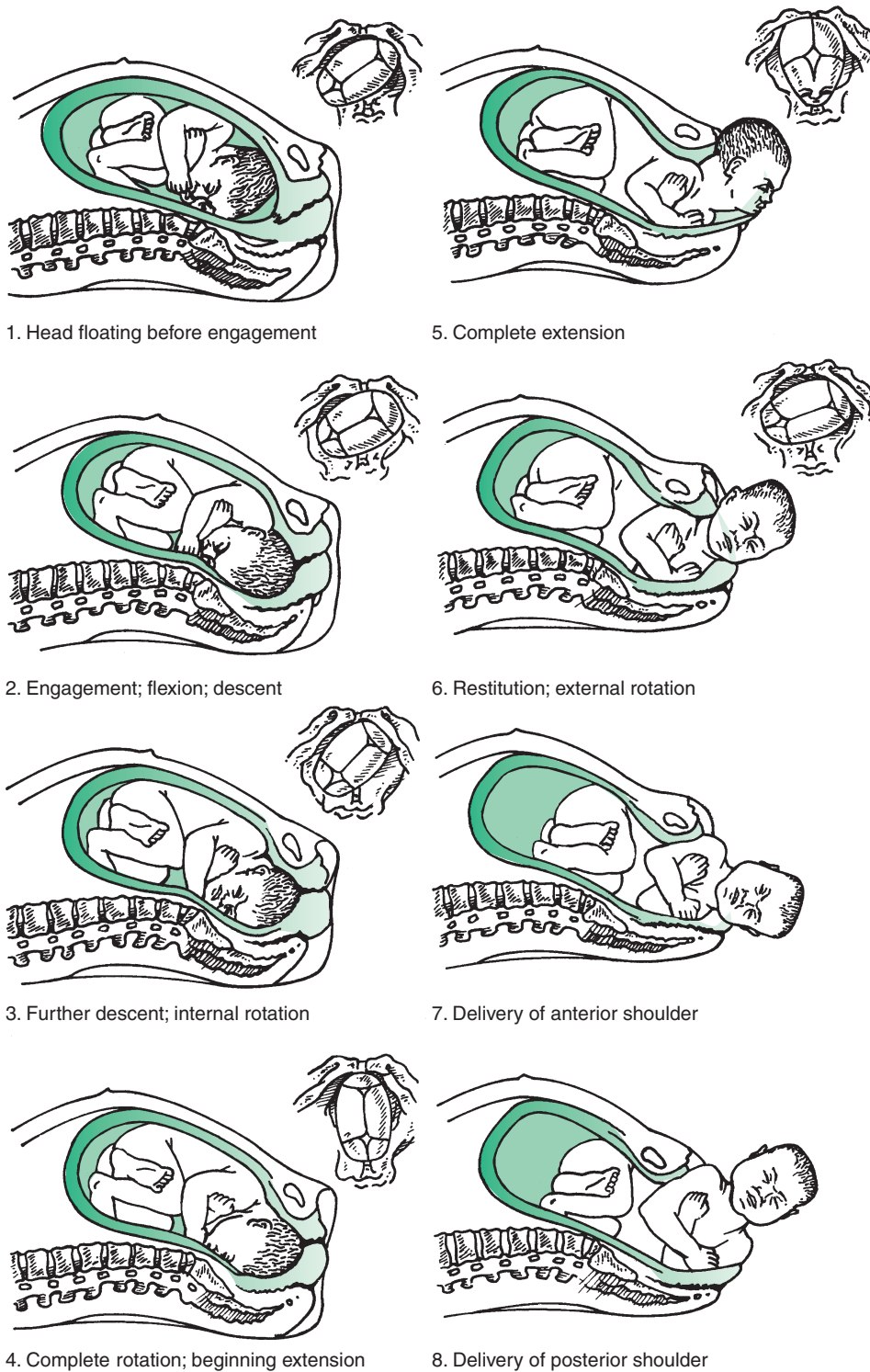


FIGURE 10-2 Principal movements in labor and delivery, left occiput anterior position. (From Cunningham FG, MacDonald PC, Gant NF. *Williams Obstetrics*. 21st Ed. New York: McGraw-Hill, 2001:302, Figure 12-13.)

7. *Expulsion.* After external rotation, the anterior shoulder appears under the symphysis and is delivered. The perineum soon becomes distended by the posterior shoulder. After delivery of the shoulders, the rest of the infant's body is extruded quickly.

IV

CONDUCT OF LABOR

- A Identification of labor** Distinguishing between true labor and false labor, detection of rupture of membranes (Table 10–1).
1. Contractions of true labor cause discomfort mainly in the back and upper abdomen, gradually intensify, occur at regular intervals, and are not stopped by sedation. The interval between the contractions gradually shortens and all of the above ultimately results in progressive cervical dilation or change. Conversely, contractions of false labor cause discomfort mainly in lower abdomen, occur at irregular intervals, do not intensify with time, and can be relieved by sedation. Interval between contractions remains long and therefore does not result in cervical change or dilation. In instances when a labor diagnosis cannot be established initially with certainty, a longer period of observation may be warranted.
 2. Detection of rupture of membranes. Conclusive diagnosis of rupture of membranes is made when amniotic fluid is seen pooling in the posterior fornix or clear fluid is passing from the cervical canal. In a term pregnancy, labor is likely to occur soon after membrane rupture. Once membranes are ruptured, expeditious delivery is desirable to prevent intraamniotic infection. Membrane rupture can be confirmed with:
 - a. Pooling—Upon sterile speculum examination, a pool of amniotic fluid may be present and visible at the vaginal vault.
 - b. Nitrazine “dye” test—Nitrazine paper changes color, depending on the pH of the fluid being tested. Amniotic fluid, which is alkaline, turns Nitrazine paper deep blue. False-positive tests can occur with blood, semen, or bacterial vaginosis. False-negative tests can occur with minimal fluid or pool in the vagina.
 - c. Ferning—Amniotic fluid, like many body fluids, has a high sodium content, which causes a ferning pattern when the fluid is air dried on a slide. Other vaginal or cervical secretions do not have such a ferning pattern. This is the most sensitive way to confirm membrane rupture.
 3. Cervical examinations. A cervical examination (determination of dilation, effacement, station), or serial cervical examinations, can be used to determine if a woman is active labor. They are also performed periodically throughout the labor course to follow a woman's progress, usually at 2- to 3-hour intervals. However, one should try to limit the number of cervical examinations during labor, as the number of examinations does correlate with infectious morbidity, especially in cases of early membrane rupture.
- B Electronic fetal monitoring** The fetal heart rate and frequency of contractions are monitored intermittently or continuously throughout the course of labor. This is done to ensure fetal well-being during the labor course (See Chapter 11).
- C First stage of labor** On average, the first stage of labor lasts for approximately 12 hours in the primigravida and approximately 7 hours in the multigravida, although there is great patient-to-patient variability.

TABLE 10–1 True Versus False Labor

	True Labor	False Labor
Contractions	Regular intervals 2 to 4 minutes apart; intensity gradually increases and can last for 1 minute	Irregular intervals; no pattern; intensity remains steady
Discomfort	Back and abdomen	Lower abdomen
Dilation	Progressive	No change in cervix
Effect of sedation	Contractions are not affected	Contractions are relieved or stopped

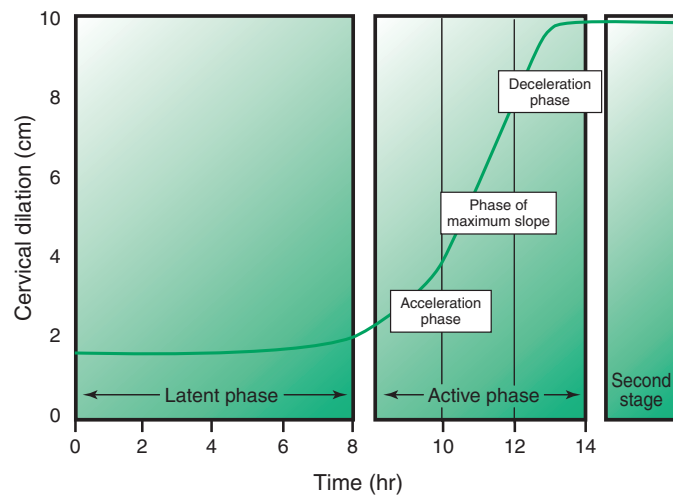


FIGURE 10-3 Composite of the average dilation curve for nulliparous labor. The first stage is divided into a relatively flat latent phase and a rapidly progressive active phase. In the active phase, three identifiable component parts include an acceleration phase, a linear phase of maximum slope and a deceleration phase. (From Pritchard JA, MacDonald PC, Gant NF. Williams Obstetrics. 21st Ed. New York: McGraw-Hill, 2001:428, Figure 18-4.)

1. The first stage of labor is divided into a latent phase and an active phase. The *Friedman curve* is frequently used in the first and second stage of labor, to chart labor progress, thus providing a framework for whether labor is progressing normally or abnormally. By the Friedman curve, the first stage of labor is divided into a latent phase and a more rapidly progressive active phase (Fig. 10-3 and Tables 10-1 and 10-2).
 - a. *Latent phase of labor.* During the latent phase, the uterine contractions can vary in intensity and frequency, but are sufficient to result in slow dilation and effacement of the cervix. A prolonged latent phase is more than 20 hours in the primigravida and more than 14 hours in the multigravida.

TABLE 10-2 Abnormal Labor Patterns, Diagnostic Criteria, and Methods of Treatment

Diagnostic Criteria				
Labor Pattern	Nulliparas	Multiparas	Preferred Treatment	Exceptional Treatment
Prolongation disorder (prolonged latent phase)	>20 hours	>14 hours	Therapeutic rest for urgent problems	Oxytocin or cesarean delivery
Protraction Disorders				
Protracted active phase dilatation	<1.2 cm/hr	<1.5 cm/hr		
Protracted descent	<1.0 cm/hr	<2 cm/hr	Expectant management	With CPD: cesarean delivery and support
Arrest Disorders				
Prolonged deceleration phase	>3 hours	>1 hour	Without CPD: oxytocin	Rest if exhausted
Secondary arrest of dilatation	>2 hours	>2 hours		
Arrest of descent	>1 hour	>1 hour	With CPD: cesarean delivery	Cesarean delivery
Failure of descent	No descent in deceleration phase of second stage of labor	Cesarean delivery	Cesarean delivery	

CPD, cephalopelvic disproportion.

From Cunningham FG, MacDonald PC, Gant NF. Williams Obstetrics. 21st Ed. New York: McGraw-Hill, 2001:431, Table 18-4.

- b. *Active phase of labor.* The active phase, or the rapidly progressive phase of labor, is characterized by progressive cervical dilation. It has three identifiable components: an acceleration phase, a linear phase of maximum slope, and a deceleration phase. A prolonged active phase is seen in the primigravida who dilates less than 1.2 cm/hr and in the multigravida who dilates less than 1.5 cm/hr.
- 2. If labor needs to be induced, for either maternal or fetal indications or for ruptured membranes after 34 weeks' gestation, occasionally the cervix may not "favorable." It may need to be prepared, in order to increase success of labor induction and vaginal delivery.
 - a. *Bishop's score* determines the favorability of the cervix, and the risk of induction failure with an unripened cervix not be ripened. It takes into account the following variables: cervical dilation, cervical effacement, cervical consistency, cervical locations, and station of fetal vertex. See chapter 14 for Bishop's Score chart.
 - b. Agents used for cervical ripening:
 - (1) Hormonal: Prostaglandin E1 (Misoprostol, aka cytotec), Prostaglandin E2 (Dinoprostone, aka Prepidil gel, and cervidil insert)
Note: Prior c-section is a contraindication to use of these above hormonal ripening agents.
 - (2) Mechanical: Foley bulb is inserted through the cervix into uterine cavity. The Foley bulb is then filled with approximately 30cc of normal saline, and gentle tension is applied to the catheter so that the bulb sits at the level of the internal os.
- 3. Management of the first stage of labor
 - a. Expectant management of labor—when a woman presents in active labor, oftentimes regular contractions will result if progressive cervical dilation and lead to the second stage of labor, without any need for medical interventions or augmentation.
 - b. Labor augmentation—lack of labor progression, as determined by the Friedman curve, requires labor augmentation, with the hopes of labor progress to the second stage of labor. Available methods include:
 - (1) Amniotomy—artificial rupture of the membranes can shorten the length of labor. However, if this procedure is done when the head is not well applied to the cervix, a cord prolapse can result. Also, if done too early in the labor process, can increase the risk of chorioamnionitis.
 - (2) Oxytocin (pitocin) administration—continuous, intravenous infusion of a dilute synthetic oxytocin solution is often used to increase contractions, thereby actively managing labor or treating dysfunctional labor patterns. During pitocin administration, the fetal heart tracing must be monitored continuously, to ensure that the fetus can tolerate increased frequency or intensity of contractions.
 - c. If labor augmentation does not result in progression to the second stage of labor, assessment for an arrest disorder of labor must occur. Placement of an intrauterine pressure catheter is performed for determining the adequacy of uterine contractions, as calculated by Montevideo units (mVu).
 - (1) Montevideo units are used to determine the adequacy of uterine contractions in the active phase of labor only. Montevideo units are calculated by subtracting the baseline uterine pressure from the peak contraction pressure for each contraction in a 10-minute period.
 - (a) If less than 200 mVu are present, treatment for this protracted labor course is additional administration of pitocin.
 - (b) If greater than 200 mVu are present, progressive cervical dilation and achievement of the second stage of labor should occur.
 - (2) If progression of active labor does not occur with "adequate" contractions, an arrest of active phase is present and c-section delivery is indicated.

D Second stage of labor On the average, the second stage lasts for approximately 50 minutes in the primigravida and approximately 20 minutes in the multigravida. However, the second stages that last 2 hours, especially in the primigravida, are common. The second stage is characterized by intense pushing on the part of the patient.

1. Spontaneous vaginal delivery
 - a. Delivery of the head. With each contraction, the vulvar opening is dilated by the head. The encirclement of the largest diameter of the fetal head by the vulvar ring is known as crowning.
 - b. Delivery of the shoulders. In most cases, the shoulders appear at the vulva just after external rotation and are delivered spontaneously. If the shoulders are not delivered spontaneously, gentle traction is used to engage and deliver the anterior and then the posterior shoulders. Excessive traction with extension of the infant's neck can result in temporary or permanent injury to the brachial plexus, known as Erb's palsy.
2. Episiotomy involves an incision in the perineum that is either in the midline (median episiotomy) or begun in the midline but directed laterally away from the rectum (mediolateral episiotomy). While it may occasionally be performed, this procedure should not be done routinely to facilitate delivery. It is now clear that an episiotomy will increase the risk of a tear into the external anal sphincter and/or the rectum.

E Third stage of labor The placenta usually is delivered within 5 minutes of the delivery of the infant.

1. Signs of placental separation
 - a. The uterus becomes globular and firm.
 - b. A sudden gush of blood.
 - c. The uterus rises in the abdomen. As the placenta, having separated, passes down into the lower uterine segment and vagina, its bulk pushes the uterus upward.
 - d. The umbilical cord protrudes farther out of the vagina, indicating that the placenta has descended.
2. Uterine hemostasis. The mechanism by which hemostasis is achieved at the placental site is **vasoconstriction**, produced by a well-contracted myometrium. Intravenous or intramuscular **oxytocin** (10 U intramuscularly or 20 U in a 1,000-mL intravenous bottle), **ergonovine** (0.2 mg intramuscularly or intravenously), or **prostaglandin F_{2a}** (0.25 mg intramuscularly and repeated if necessary at 15- to 90-minute intervals up to a maximum of eight doses) helps the uterus contract and decreases blood loss. These medications are administered after the placenta has been delivered.

F Lacerations of the birth canal There are four types of vaginal or perineal lacerations:

1. *First-degree lacerations* involve the fourchette, perineal skin, and vaginal mucosa, but not the fascia and muscle.
2. *Second-degree lacerations* involve the skin, mucosa, fascia, and muscles of the perineal body, but not the anal sphincter.
3. *Third-degree lacerations* extend through the skin, mucosa, perineal body, and involve the anal sphincter.
4. *Fourth-degree lacerations* are extensions of the third-degree tear through the rectal mucosa to expose the lumen of the rectum.



Study Questions for Chapter 10

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A 26-year-old woman, gravida 2, para 1, at 39 weeks of gestation, is admitted to the hospital in labor with ruptured membranes. Her cervix is dilated 5 cm and is 100% effaced, and fetal vertex is at +1 station. You place a fetal scalp monitor and an intrauterine pressure catheter. Fetal monitoring strip reveals five contractions in 10 minutes, and each contraction produces 50 mm Hg of pressure. Three hours later, her cervix is 5 cm dilated and 100% effaced, and fetal vertex is at +1 station. What is the next best step in management?

- ☐ A Augmentation with oxytocin
- ☐ B Cesarean section
- ☐ C Vacuum delivery
- ☐ D Magnesium sulfate
- ☐ E Methergine

2. A 22-year-old woman, gravida 1, para 0, at 40 weeks of gestation, presents to labor and delivery reporting regular contractions for the last 2 hours. She denies loss of fluid from the vagina and reports good fetal movement. Her cervix is dilated 2 cm and 50% effaced, and fetal vertex is at 0 station. The fetal monitoring strip shows regular uterine contractions every 2 to 3 minutes. The fetal heart rate baseline is 154 bpm without decelerations and is reactive. What is the next step in management?

- ☐ A Cesarean section
- ☐ B Oxytocin
- ☐ C Fundal massage
- ☐ D Walk for 1 to 2 hours then return to check her cervix
- ☐ E Meperidine

3. A 29-year-old woman, gravida 2, para 1, at 32 weeks of gestation, presents to labor and delivery reporting flank pain, fever, chills, and cramping. She is having contractions every 3 to 4 minutes, and the fetal heart rate baseline is 180. You check her cervix and discover a dilation of 3 cm and 100% effacement, and you see that the fetal head is floating. From the physical examination and from results of the urinalysis, you conclude that she has pyelonephritis and admit her to the hospital for intravenous antibiotics, magnesium sulfate to try to slow contractions, and steroids. Several hours later, you are paged because she is having trouble breathing. Her vitals are as follows: T = 102.1, BP = 110/78, P = 105, R = 28, and oxygen saturation is 96% on room air. Physical examination reveals that her heart is tachycardic but without murmurs. You hear bilateral rales over the lung bases. Her abdomen is soft, gravid, and nontender. She still has costo-vertebral angle tenderness. There is 2+ pedal edema. Which of the following is the most likely diagnosis?

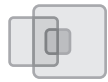
- ☐ A Complication of pyelonephritis
- ☐ B Congestive heart failure
- ☐ C Pulmonary embolus
- ☐ D Pulmonary edema
- ☐ E Respiratory muscle paralysis

4. A 24-year-old woman, gravida 1, para 0, at 39 weeks of gestation, is crowning. The fetal head is not emerging from the vagina after two pushes. You palpate a thick hymenal ring of tissue at the introitus. Fetal monitoring strip shows bradycardia after the third push, so you decide to cut a 3-cm episiotomy that extends through the hymenal ring and vagina and ends laterally in the perineum. What is the advantage of this type of episiotomy?

- ☐ A Clean surgical incision
- ☐ B Avoids fourth-degree laceration
- ☐ C Less dyspareunia
- ☐ D Commonly used when distance between posterior introitus and anus is large
- ☐ E Easier to repair

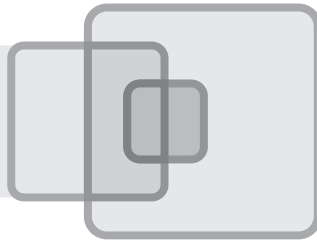
5. A professor of obstetrics is explaining the seven cardinal movements of labor: first—the greatest transverse diameter of the fetal head passes through the pelvic inlet; second—the fetal head descends; third—the fetal chin is brought into close contact with the fetal thorax; fourth—turning of the occiput toward the 12 o'clock position; fifth—the uterine contractions extend the fetal vertex anteriorly. What is the next step?

- ☐ A Delivery of the head
- ☐ B Rotation of occiput to transverse position
- ☐ C Rotation of occiput to posterior position
- ☐ D Delivery of anterior shoulder
- ☐ E Expulsion



Answers and Explanations

1. **The answer is B** [IV C; Table 10–2]. This is a clinical scenario where the patient has had arrest of dilation (i.e., there has been no change in dilation in the last 2 hours in this multiparous patient). Augmentation with oxytocin is not necessary because she has adequate contraction frequency (every 2 to 3 minutes) and intensity (50 mm Hg) in a 10-minute period. This patient is not a candidate for vacuum delivery. To perform a low vacuum delivery, the cervix must be fully dilated, the station must be +2 or greater, the rotation of the fetal head is unnecessary, and a valid indication for use of vacuum must be present (i.e., fetal distress, prolonged second stage of labor, or maternal disease process [e.g., heart condition or brain aneurysm], which benefit from reduction in pushing during the second stage of labor). There is no need to use a tocolytic to slow down labor. You want to achieve the opposite. Methergine is used for postpartum hemorrhage.
2. **The answer is D** [II D; Table 10–1]. This patient is in the first stage, the latent phase, of labor. It is difficult to predict when a person will make the transition from the latent phase to active phase of labor. At this point, you cannot tell if this patient is in true labor or if this is false labor. By having the patient walk for 1 to 2 hours and then return so you can check her cervix, you are able to diagnose labor if the cervical dilation changes. For example, if she returns in 2 hours and her cervix is dilated to 4 cm, then you can diagnose labor because her regular uterine contractions have produced cervical change. There is no need to augment her contractions with oxytocin in this stage of labor. She is not a candidate for cesarean section because there are no fetal or maternal indications. A fundal massage is a maneuver useful immediately after delivery of the placenta to help contract the uterus. Meperidine would be useful if the patient had prolongation of the latent phase of labor, that is, if she was having regular, painful uterine contractions for more than 20 hours (in nulliparas = “para 0”) and did not have a change in her cervix.
3. **The answer is D.** This patient has many risk factors for noncardiogenic pulmonary edema. She has pyelonephritis and has been given magnesium sulfate (known to have pulmonary edema as a complication). She has bilateral lung rales because of exudation of fluid from the capillaries into the alveoli of the lung bases. There is no reason to think she has a heart problem (she is young, there is no mention of family history, heart examination is normal, and pedal edema is found in normal pregnancy). Pulmonary embolism is always a possibility and must be ruled out because she is pregnant and has tachypnea, but it is lower down in the differential diagnosis. Pyelonephritis can lead to sepsis and adult respiratory distress syndrome, but again this is lower down in the differential because there is no mention of blood culture results, her blood pressure is stable, oxygen saturation is high, and there is no mention of her level of distress. Respiratory muscle paralysis occurs at very high levels of magnesium sulfate (there is no mention of her serum magnesium level).
4. **The answer is B** [IV C 2]. A mediolateral episiotomy is cut if there is not enough space in the introitus for emergence of the fetal head and if there is a short distance between the posterior introitus and anus (because a median episiotomy has a high risk of extending into the anal sphincter and even rectal mucosa). A median episiotomy is easier to repair, has less blood loss, causes less dyspareunia, heals better, and has better anatomic results. Clean surgical incision is obtained with both median and mediolateral episiotomy.
5. **The answer is B** [III B 6]. The sixth cardinal movement begins with delivery of the fetal head by extension and ends with rotation of the occiput from the anterior position to the oblique and then to the transverse position. Expulsion and delivery of the anterior shoulder is the seventh cardinal movement.



Intrapartum Fetal Monitoring

MATTHEW N. BESHARA

I

INTRODUCTION

- A** The **fetal heart rate (FHR)** is under the control of the autonomic nervous system (ANS). An intact ANS reflects the interplay between the sympathetic and parasympathetic nervous systems. This results in the rise and fall of the FHR from baseline, also known as *variability*—this variability is an indication of **normal fetal oxygenation**.
- B** **Intrapartum FHR monitoring** is used to **assess fetal well-being** during labor. It closely **quantifies and interprets the FHR** to obtain reassurance that fetal oxygenation is normal.
1. A **reassuring FHR pattern** is associated with **adequate oxygenation** of the fetus and a newborn that is vigorous at birth. When the FHR pattern is **reassuring**:
 - a. A clinician can safely allow labor to proceed.
 - b. There is a **low risk of perinatal asphyxia**, which refers to **damaging acidemia, hypoxia, and metabolic acidosis** associated with **neonatal neurologic sequelae** and other organ dysfunction.
 2. A **nonreassuring FHR pattern** is a sign of potential **hypoxia**. When the FHR pattern is **nonreassuring**:
 - a. A clinician must obtain other reassurance of fetal well-being.
 - b. It may be necessary to expedite delivery.

II

PATHOPHYSIOLOGY OF FETAL HYPOXIA

- A** **Normal fetal oxygenation**
1. Uterine blood flow, intervillous blood flow, and transplacental gaseous exchange are reduced during normal labor, temporarily resulting in relative fetal hypoxemia.
 2. Transient, sometimes repetitive, episodes of hypoxemia and hypoxia, even at the level of the central nervous system (CNS), are common during normal labor and are usually well tolerated by the fetus.
 3. Greater fetal oxygen-carrying capacity allows adequate delivery of oxygen to the fetal tissues despite the low fetal arterial partial pressure of oxygen (PO_2) for the following reasons:
 - a. Higher fetal cardiac output
 - b. Higher systemic blood flow rate (compared with adults)
 - c. Greater affinity of fetal hemoglobin for oxygen
- B** **Fetal hypoxia**
1. When uterine or umbilical blood flow is impaired, fetal tissue perfusion is decreased and **oxygen transfer is diminished**.
 2. Carbon dioxide accumulates in the fetal circulation, causing a **decline in pH, resulting in acidemia**.
 3. Prolonged periods of decreased uterine or placental perfusion lead to **metabolic acidosis** as the fetus becomes dependent on anaerobic glycolysis to meet its energy requirements.

4. As pyruvic and lactic acids accumulate, there is a further drop in fetal pH, eventually resulting in **asphyxia** if unresolved.

III

TYPES OF FETAL HEART RATE MONITORING

- A Continuous monitoring** The FHR pattern can be continuously evaluated in two ways.
1. An **external ultrasound device** placed on the maternal abdomen emits and receives the reflected **ultrasound signal from the movement of the fetal heart valves**. The reflected sound waves return to the transducer, permitting an assessment of the FHR activity.
 2. A **fetal scalp electrode** measures **consecutive R–R wave intervals** of the fetal QRS complex, directly measuring the FHR. The signal is transmitted to a monitor, where it is amplified, counted, and recorded.
- B Intermittent FHR auscultation** A fetoscope is placed on the maternal abdomen similar to a stethoscope. This method is **equivalent to continuous monitoring** in assessing fetal condition when performed at specific intervals with a 1:1 nurse–patient ratio. A fetoscope is rarely used in modern medicine and electronic intermittent auscultation is utilized. Continuous electronic monitoring is more commonly used in the United States because it is convenient and less labor intensive without the added expense for staffing.
1. During the **active phase of labor**, auscultation is recorded **at least every 15 minutes** after a contraction
 2. During the **second stage of labor**, auscultation is recorded **every 5 minutes**.

IV

INTERPRETATION OF FETAL HEART RATE PATTERNS

When describing the FHR tracing in labor, the clinician evaluates the **baseline FHR, variability, contraction frequency, and periodic changes**.

- A Baseline FHR** The FHR is the heart rate that occurs between contractions, regardless of accelerations or decelerations.
1. **Normal**
 - a. **Normal baseline FHR is 110 to 160 beats per minute (bpm).**
 - b. The baseline FHR decreases gradually from 16 weeks' gestation to term as the parasympathetic system develops.
 2. **Tachycardia**
 - a. **Baseline tachycardia** is an **FHR greater than 160 bpm** for periods of 10 minutes or more.
 - b. Recurrent tachycardia can be associated with the following conditions:
 - (1) Hypoxia
 - (2) Maternal fever
 - (3) Chorioamnionitis (inflammation and infection of the fetal membranes)
 - (4) Prematurity
 - (5) Drugs (e.g., terbutaline, atropine)
 - (6) Fetal stimulation (e.g., digital stimulation of the fetal head)
 - (7) Fetal arrhythmias
 - (8) Maternal anxiety
 - (9) Maternal thyrotoxicosis
 3. **Bradycardia**
 - a. **Baseline bradycardia** is an **FHR less than 110 bpm** for periods of 10 minutes or more.
 - b. Recurrent bradycardia can be associated with the following conditions:
 - (1) Hypoxia
 - (2) Drugs (e.g., mepivacaine, beta-blockers)
 - (3) Autonomic-mediated reflex (e.g., to pressure on fetal head)
 - (4) Arrhythmias
 - (5) Hypothermia
 - (6) Maternal hypotension

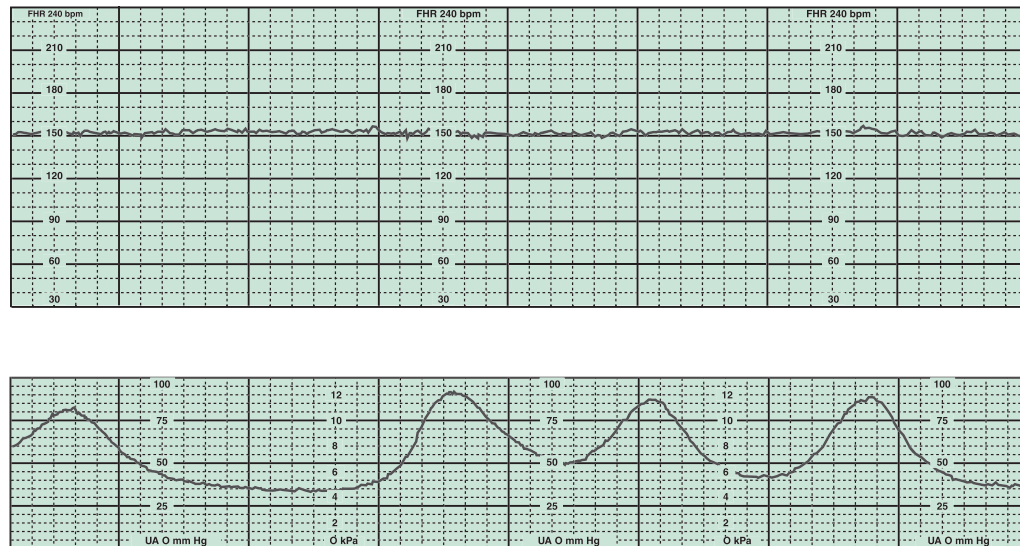


FIGURE 11-1 Minimal variability.

B FHR variability

1. **Baseline variability** is defined as deflections from the baseline FHR resulting from the continuous interaction between fetal sympathetic and parasympathetic nervous systems. **Normal variability** is one of the best indicators of **intact integration** between the fetal CNS and the heart.
2. Causes of **loss of variability**
 - a. **Hypoxia**
 - b. Fetal sleep state (sleep cycles of 30 minutes or less)
 - c. CNS depressants (e.g., atropine, scopolamine, tranquilizers, narcotics, barbiturates, anesthetics)
 - d. Prematurity
 - e. Baseline tachycardia
 - f. Fetal cardiac abnormalities or arrhythmias
 - g. Fetal CNS abnormalities
3. Characterization of variability
 - a. **Absent:** undetectable amplitude
 - b. **Minimal** (Fig. 11-1): detectable amplitude but less than 5 bpm
 - c. **Moderate** (Fig. 11-2): amplitude of 6 to 25 bpm
 - d. **Marked:** amplitude of more than 25 bpm

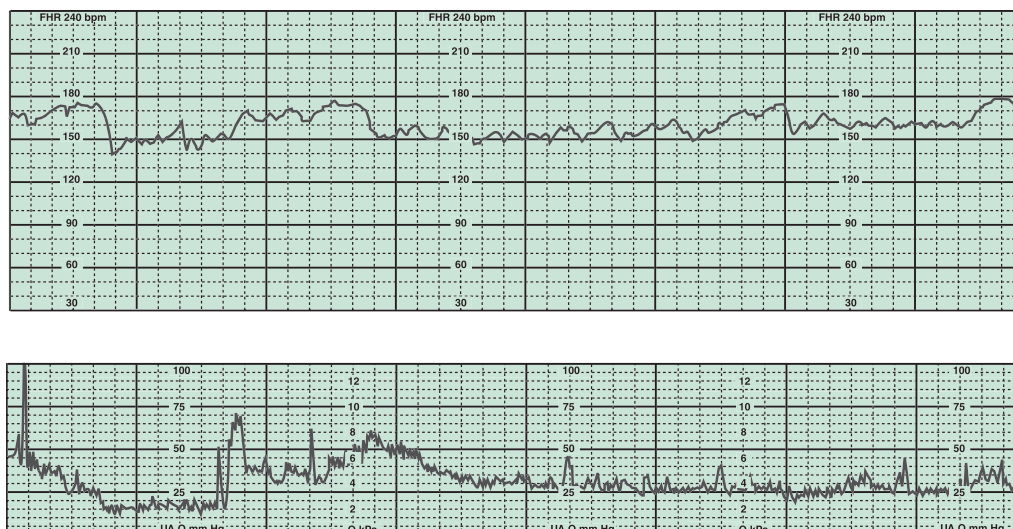


FIGURE 11-2 Moderate variability.

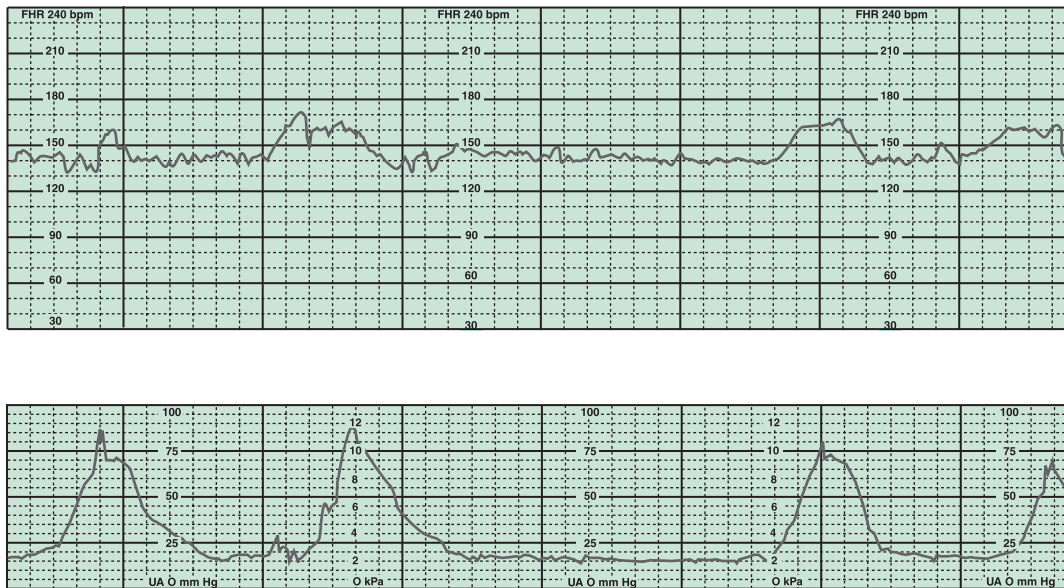


FIGURE 11-3 Accelerations are defined as abrupt increases in baseline FHR, which peak in less than 30 seconds.

C Contractions Assessment occurs in two ways.

1. **Tocodynamometer**

- A pressure-sensitive tocodynamometer is placed around the maternal abdomen.
- The tocodynamometer measures **only the frequency of contractions**, not their intensity or strength.

2. **Intrauterine pressure catheter (IUPC).** This method allows internal monitoring of contractions.

- After the catheter is introduced into the uterine cavity, it is attached to a strain gauge, which measures the pressure generated by the uterine contractions.
- IUPC measures **both the frequency and the strength of contractions**.

D FHR accelerations (Fig. 11-3) are defined as abrupt increases in baseline FHR (onset to peak FHR in less than 30 seconds).

- Before 32 weeks' gestation**, accelerations are defined as having a peak of **at least 10 bpm** above baseline, **lasting for 10 seconds or more**.
- After 32 weeks' gestation**, accelerations are defined as having a peak of **at least 15 bpm** above baseline, **lasting between 15 seconds and 2 minutes**.

E FHR decelerations The **three patterns of periodic decelerations** are based on the waveform configuration and the **timing of the deceleration in relation to the uterine contraction**.

1. **Early decelerations** (Fig. 11-4)

- Definition.** Early decelerations begin with the onset of uterine contractions, **reach their lowest point (never less than 100 bpm) at the peak of the contraction**, and return to baseline as the contraction ends.
- Mechanism.** Early decelerations are thought to be caused by local changes in cerebral blood flow, which result in stimulation of the **vagal centers**, with acetylcholine release at the sinoatrial node.
- Associated conditions.** Early decelerations can occur when the **fetal head is compressed** as it moves down the birth canal. The decelerations are considered physiologic and are **not associated** with fetal acidemia.

2. **Variable decelerations**

- Definition.** Variable decelerations are **abrupt decreases in FHR** with a rapid return to baseline (onset of deceleration to nadir less than 30 seconds) that may **occur before, during, or after** the onset of uterine contractions.

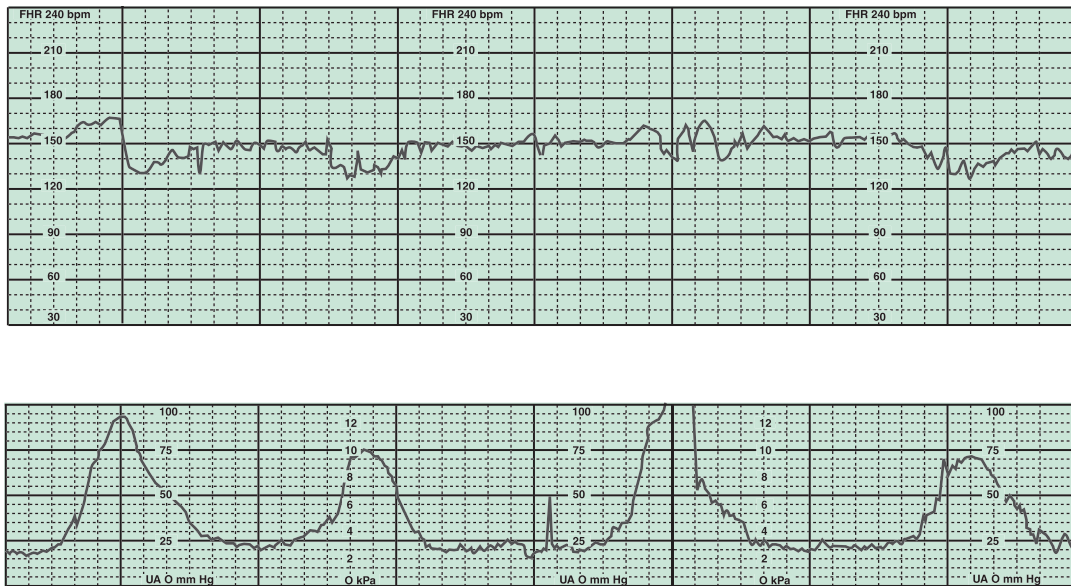


FIGURE 11-4 Early decelerations reach their lowest point at the peak of the contraction.

- b. Mechanism.** Variable decelerations involve **reflex-mediated changes** in the FHR controlled by the vagus nerve.
- c. Associated conditions.** Variable decelerations are generally caused by **umbilical cord compression** between fetal parts or between fetal parts and the uterine wall. They can also be seen in patients with **oligohydramnios**.
- d. Types of variable decelerations**
 - (1) **Mild** (Fig. 11-5)
 - (a) Duration of less than 30 seconds
 - (b) Minimal clinical significance
 - (2) **Moderate** (Fig. 11-6)
 - (a) Two types
 - (i) Nadir of 70 to 80 bpm, with duration of more than 60 seconds
 - (ii) Nadir of less than 70 bpm, with duration of 30 to 60 seconds
 - (b) Persistent moderate variable decelerations can lead to a reduction in fetal oxygenation, resulting in hypoxemia and acidemia.

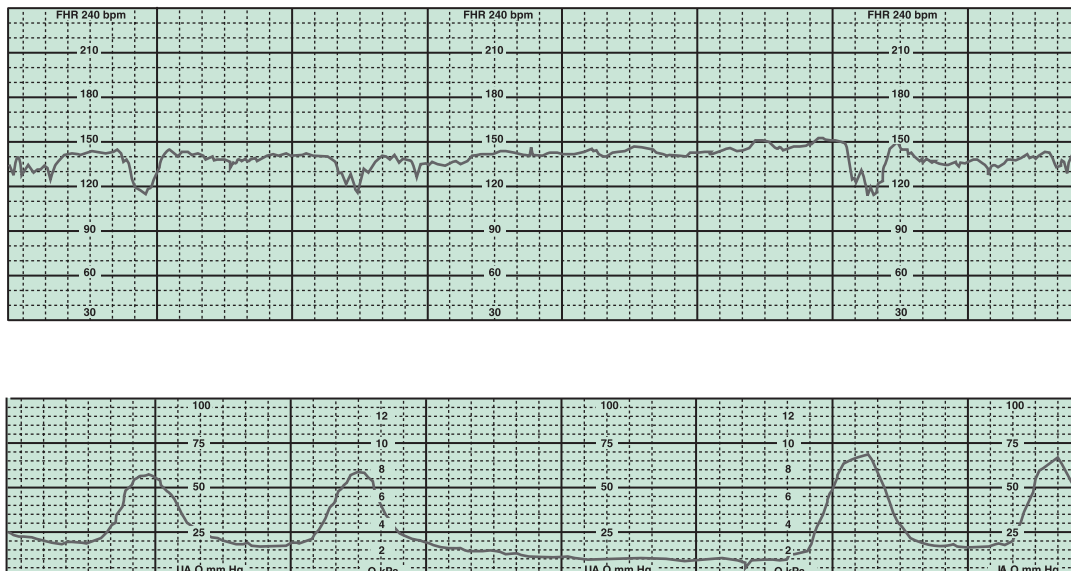


FIGURE 11-5 Mild variable decelerations last less than 30 seconds.

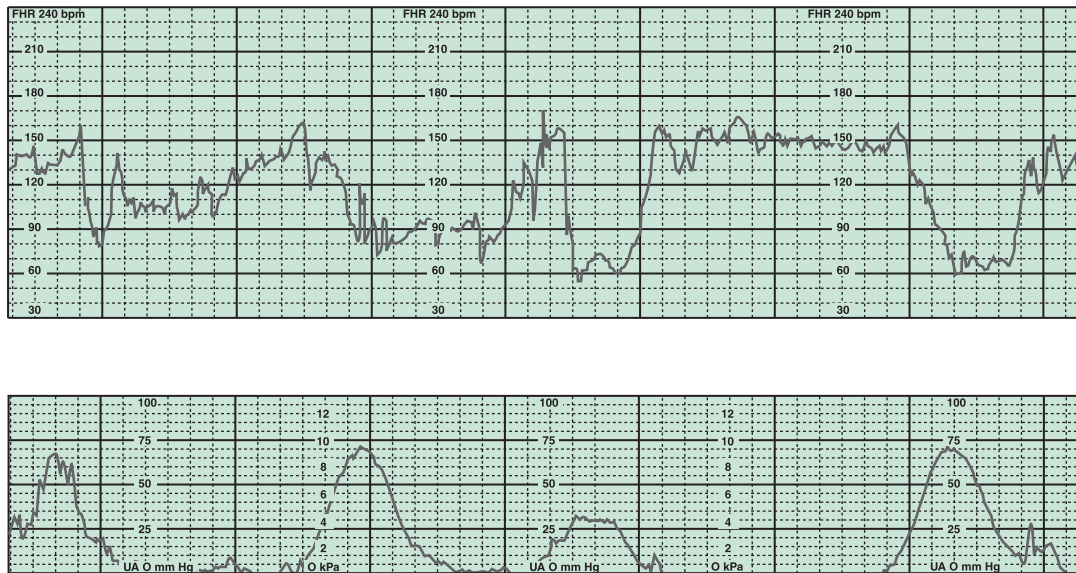


FIGURE 11-6 Moderate and severe variable decelerations.

(3) **Severe** (Fig. 11-6)

- (a) Nadir of less than 70 bpm, with duration of more than 60 seconds
- (b) Prolonged or severe variable decelerations may lead to a significant reduction in respiratory gas exchange with subsequent fetal hypoxemia and acidemia

3. **Late decelerations** (Fig. 11-7)

a. **Definition.** Late decelerations are gradual decreases and returns to baseline FHR associated with uterine contractions (onset to nadir is 30 seconds or more). The **nadir occurs after the peak of the contraction.**

b. **Mechanism and associated conditions**

- (1) Late decelerations associated with **normal variability** represent reflex responses mediated via the vagus nerve. They may be seen with **mild transient hypoxia.**
- (2) Late decelerations associated with **decreased variability** can result from direct myocardial depression and can be seen with **prolonged hypoxia and acidemia.**

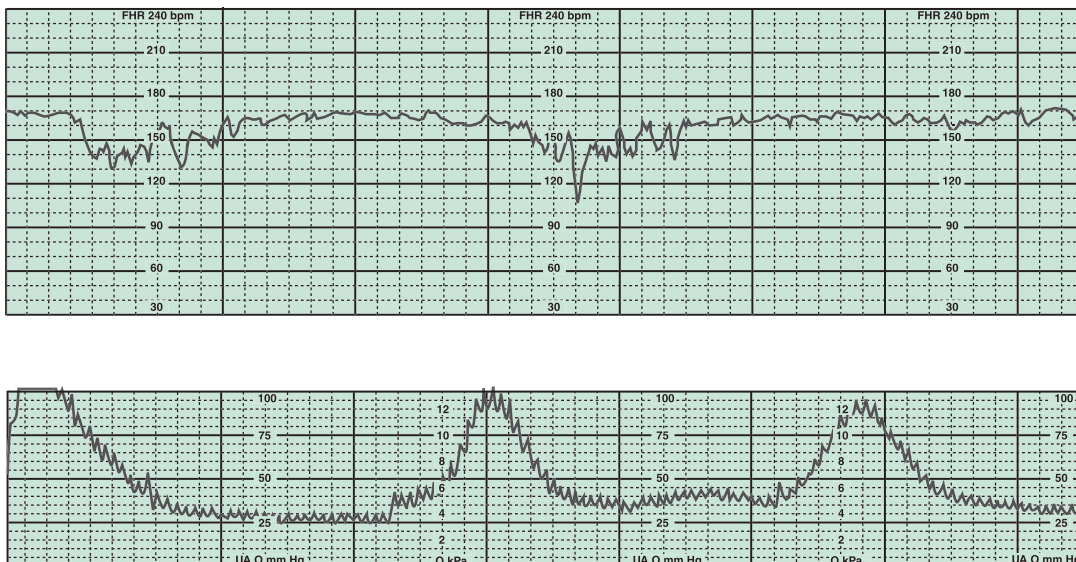


FIGURE 11-7 Late decelerations. The nadir of each deceleration occurs after the peak of the contraction.

- (3) **Uteroplacental insufficiency**, which results from decreased uterine perfusion or decreased placental function, can lead to repetitive late decelerations and minimal variability. Conditions that may lead to uteroplacental insufficiency include:
 - (a) Postdates pregnancy
 - (b) Maternal diabetes mellitus
 - (c) Maternal hypertension (chronic or pregnancy induced)
 - (d) Abruptio placentae
 - (e) Maternal anemia
 - (f) Maternal sepsis
 - (g) Hypertonia (excessive uterine tone)
 - (h) Hyperstimulation (excessive uterine contractions)
- 4. **Prolonged decelerations**
 - a. **Definition.** Prolonged decelerations are decreases from baseline of 15 bpm or more that last 2 to 10 minutes.
 - b. **Mechanism.** Prolonged decelerations can result from the following factors:
 - (1) **Vagus nerve discharge** (e.g., head compression during rapid descent)
 - (2) **Fetal hypoxia** caused by mechanisms such as:
 - (a) Uterine hyperactivity
 - (b) Sympathetic blockade from regional anesthesia
 - (c) Supine hypotension
 - (d) Unrelieved cord compression
 - (e) Maternal respiratory arrest

V

CLASSIFICATION OF FETAL HEART RATE TRACINGS, THREE TIER

A Category I:

- 1. FHR tracings include all of the following:
 - a. Baseline rate, 110 to 160 bpm
 - b. Baseline FHR variability classified as “moderate”
 - c. Accelerations: present or absent
 - d. Late and variable decelerations are absent
 - e. Early decelerations can be present or absent

B Category II:

- 1. This category is all tracings that are not categorized as Category I or II

C Category III:

- 1. FHR tracings include the following:
 - a. Absent baseline FHR variability plus
 - (1) Recurrent late decelerations
 - (2) Recurrent variable decelerations
 - (3) Bradycardia
 - b. Sinusoidal pattern

VI

FETAL HEART RATE TRACINGS: ASSESSMENT AND MANAGEMENT IN LABOR

- A** **Reassuring FHR patterns** When FHR tracings are reassuring, practitioners allow labor to continue. FHR accelerations contribute to the reassurance of fetal well-being.

B **Nonreassuring FHR patterns**

- 1. **Characteristics**
 - a. Repetitive decelerations
 - b. Abnormal baseline FHR
 - c. Absence of accelerations
 - d. Loss of variability

- e. Repetitive late decelerations; repetitive, moderate-to-severe variable decelerations; and absent variability or baseline tachycardia
- 2. **Further evaluation** is necessary.
 - a. Evaluate for the **potential causes** of the nonreassuring FHR pattern.
 - b. Obtain information and reassurance about the fetal well-being.
 - c. Perform intrauterine resuscitation to improve placental perfusion and oxygen transfer to the fetus.

C Management of women with nonreassuring FHR patterns

1. **Change in maternal position**
 - a. In the **supine position**, the uterus obstructs blood flow through the aorta and the inferior vena cava, potentially leading to decreased placental perfusion.
 - b. Placement in a lateral recumbent position during labor causes the uterus to fall away from the great vessels, which should improve fetal oxygenation.
2. **Oxygenation. Maternal hyperoxia** may increase the maternal–fetal oxygen gradient, potentially improving the FHR pattern. Oxygen should be given by mask.
3. **Reversal of anesthetic effects**
 - a. **Sympathetic blockade** from epidural anesthesia may result in decreased venous return and cardiac output, maternal hypotension, and decreased uteroplacental perfusion.
 - b. Administration of intravenous fluids or ephedrine to the mother may improve uterine blood flow and, therefore, the FHR tracing.
4. **Regulation of uterine activity**
 - a. **Hyperstimulation or multiple uterine contractions** from prostaglandin or oxytocin stimulation may lead to incomplete uterine relaxation and possibly decreased fetal oxygenation.
 - b. Intravenous hydration, **discontinuation of the uterotonic agent**, or uterine relaxation with terbutaline (β -sympathomimetic) may improve the FHR pattern.
5. **Correction of cord compression.** Variable decelerations, which are caused by **umbilical cord compression**, may be corrected with the following maneuvers:
 - a. Change in maternal position, which may relieve the compression.
 - b. Placement of an **amnioinfusion**, which is an intrauterine catheter through which saline is infused into the uterine cavity to alleviate some of the cord compression is sometimes used.

D Further assessment of fetal well-being After optimization of the maternal position, maternal vital signs, and labor pattern; if fetal well-being is questioned, further evaluation of fetal well-being should take place. This can be done with the following:

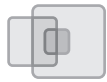
1. **Vibroacoustic stimuli (VAS).** An artificial larynx is placed on the maternal skin over the fetal head, and the fetus is stimulated by noise for 1 second.
 - a. The presence of fetal accelerations in response to VAS is considered reassuring.
 - b. The fetus is restimulated if no accelerations occur within 10 seconds. The VAS test may be repeated up to four times.
2. **Scalp stimulation test.** The examiner rubs the fetal scalp during a digital examination.
 - a. An acceleration is usually seen in the FHR tracing of the uncompromised, nonacidotic fetus. The presence of an **acceleration** is associated with an intact ANS and a fetal scalp **blood pH greater than 7.20**.
 - b. If an acceleration is not obtained after scalp stimulation, fetal scalp blood can be sampled to measure the fetal pH or one can progress to immediate surgical delivery.
3. **Fetal scalp blood sampling.** The fetal scalp is visualized through the dilated cervix, and blood is collected in heparinized capillary tubes after making a tiny stab on the scalp with a small blade. The capillary tubes are sent to the laboratory for pH measurement. The normal fetal capillary pH is 7.25 to 7.35 in the first stage of labor.
 - a. A **fetal scalp pH greater than or equal to 7.20** is reassurance that **the fetus is not acidotic**. Labor can proceed for 20 to 30 minutes.
 - (1) If a nonreassuring FHR pattern persists after 20 to 30 minutes and scalp stimulation is ineffective, the fetal scalp pH may be repeated to obtain reassurance on fetal well-being.

- (2) In the case of a nonreassuring FHR pattern, the decision to intervene depends on the clinician's assessment of the likelihood of hypoxia and the estimated time to spontaneous delivery.
- b. A **pH of less than 7.20** may represent significant **acidosis**. Delivery is thus indicated by operative (vacuum or forceps assisted) vaginal delivery, if possible, or cesarean delivery. The clinician must decide on the **most expeditious** way to deliver the baby based on the clinical circumstances.
- c. In some centers, this test is no longer performed, and if the fetal scalp stimulation test is poor, the baby is delivered immediately by cesarean section.

VII

OTHER DEVELOPMENTS IN INTRAPARTUM MONITORING: FETAL OXYGEN SATURATION MONITORING

- A** Normal fetal oxygen saturation ranges between 35% and 75%, with an average level of 55% to 60%. If the fetal oxygen saturation remains **above 30% during labor**, there appears to be **no risk of fetal metabolic acidosis**.
- B** The U.S. Food and Drug Administration approved the first device for monitoring fetal oxygen saturation. Ultimately, this device has failed to be accepted into clinical practice.
 - 1. The sensor is slid through the cervix and lodges against the fetal cheek. It is held in place by the pressure created by the fetal cheek and the pelvic sidewall.
 - 2. This method is used at some centers but has not yet been broadly instituted. (Research conducted on pulse oximetry has been suggested to decrease the false-positive rate of nonreassuring FHR patterns.)
 - 3. Some studies described decreased cesarean section rates, but overall the data have not supported this finding. The use of fetal oxygen saturation monitors is not endorsed by the American College of Obstetricians.



Study Questions for Chapter 11

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A 25-year-old woman, gravida 1, para 0, at 39 weeks of gestation, has been laboring for a few hours. Her cervix is dilated to 3 cm and 80% effaced, and fetal vertex is at 0 station. The patient has requested regional anesthesia which is delivered via epidural catheter. After placement, late decelerations are noted on the FHR monitor with a reduction in variability. Maternal blood pressure is noted to be 90/60 which is below the baseline blood pressure noted on admission. What is the best next step in management?

- ☐ A Change maternal position
- ☐ B Cesarean section
- ☐ C Maternal oxygen supplementation
- ☐ D Medication to improve maternal blood pressure
- ☐ E Amnioinfusion

2. A 27-year-old woman, gravida 1, para 0, at 40 and 3/7th weeks of gestation, is in the middle of the first stage of labor. Her cervix is dilated to 4 cm and a decision has been made to place an epidural. Prior to placement of the epidural, she receives a 500-mL bolus of lactated Ringer's to prehydrate her, and augmentation with oxytocin is begun. Her vitals are as follows: T = 99.1, BP = 110/74, P = 102, R = 18. The FHR baseline is 142 bpm with three accelerations every 20 minutes. She is contracting every 3 minutes. After placement of the epidural, FHR baseline drops to 130 bpm, and no accelerations are seen within a 10-minute period. The FHR also shows a gradual decline in the middle of each contraction to about 115 bpm and then returns to baseline of 130 bpm. She has contractions every 2 to 3 minutes now. Her vitals at this point are as follows: T = 99.2, BP = 78/56, P = 115, R = 18. What is the best next step in management?

- ☐ A Tylenol
- ☐ B Penicillin
- ☐ C Intravenous hydration
- ☐ D Ephedrine
- ☐ E Discontinue oxytocin

3. A 22-year-old woman, gravida 2, para 1, at 41 weeks of gestation, is laboring. Her cervix is dilated to 8 cm and 100% effaced, and fetal vertex is at +1 station. Membranes have been ruptured for more than 24 hours, and labor is being augmented with oxytocin. An amnioinfusion is running because of 3 to 4+ meconium. FHR by scalp electrode has a baseline of 138 bpm with reduced short-term variability and occasional mild variable decelerations. You are suddenly called to evaluate a nonreassuring FHR. The tocodynamometer shows six contractions in a 10-minute period with a pressure of 70 mm Hg, and FHR is now 70 bpm for more than 3 minutes. She is placed in the left lateral position, oxytocin infusion is stopped, she is given oxygen by mask, and her intravenous fluid rate is increased. FHR is now 98 bpm. What is the best next step in management?

- ☐ A Cesarean section
- ☐ B Vacuum delivery
- ☐ C Ephedrine
- ☐ D Knee-chest position
- ☐ E Terbutaline

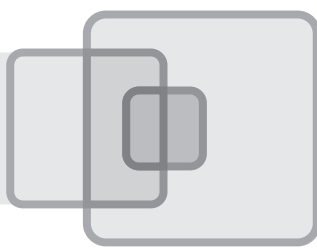
4. A 19-year-old woman, gravida 1, para 0, at 38 weeks of gestation, is in active labor. Her cervix is dilated to 5 cm and fetal vertex is at +1 station. The tocodynamometer displays contractions every 2 to 3 minutes, lasting 1 minute, and producing 50 mm Hg of pressure inside the uterus. The FHR by scalp electrode has a baseline of 140 bpm with random sharp decelerations to 70 bpm that return to baseline in 60 to 80 seconds. When this type of deceleration occurs, what is the best description of the initial acid–base status of the fetus?

- ☐ A Respiratory acidosis
- ☐ B Metabolic acidosis
- ☐ C Uteroplacental insufficiency
- ☐ D Asphyxia
- ☐ E Increased PCO_2



Answers and Explanations

1. **The answer is D** [V C 4 a and b]. This clinical scenario is describing hypotension resulting from vasodilation that can occur as a result of regional analgesia. The lower blood pressure results in decreased perfusion to the uterus, which can cause a nonreassuring FHR (in this case, late decelerations). It is possible to rectify the perfusion issue to the uterus by adjusting the maternal position, which may decrease the pressure placed on the vena cava by the gravid uterus, but this is not the best answer. If reduced blood pressure is noted after placement of regional analgesia with negative effect on the FHR tracing, prompt attention to maternal blood pressure is warranted with medication to increase blood pressure.
2. **The answer is D** [V C 4 b]. One of the complications with placement of an epidural blockade is hypotension (before the epidural BP = 110/74 and after the epidural BP = 78/56). An epidural blocks sympathetic discharge to vessel walls, and vasoconstriction is inhibited. This causes blood to pool in dependent areas of the body, thus decreasing venous return to the heart. Cardiac output decreases and subsequently results in decreased uteroplacental circulation. To avoid hypotension, anesthesiologists hydrate patients before placement of the epidural and then give ephedrine to keep the BP near its baseline. Although the patient has a low-grade temperature (99.2°F), the fever is not the cause of the nonreassuring FHR; therefore, neither Tylenol nor penicillin are the best choices. Hyperstimulation is not the problem, so there is no need to discontinue the oxytocin. This patient has already been prehydrated, so additional hydration would not be as efficacious as giving ephedrine.
3. **The answer is E** [V C 4 b]. This clinical scenario is describing hyperstimulation. Normal labor contractions have the following properties: frequency—every 2 to 3 minutes; duration—45 seconds to a minute; intensity—up to 50 mm Hg. In this case, oxytocin has already been stopped, but the nonreassuring FHR pattern has not resolved because oxytocin is still in the circulation. Thus, before taking the patient for a cesarean section, terbutaline should be tried to reverse the hyperstimulation by tocolysis. This patient is not a candidate for vacuum delivery (she is not even fully dilated yet). Ephedrine is not useful in this case. The knee–chest position is sometimes more useful than the left lateral position when there is a nonreassuring FHR pattern, especially a severe variable deceleration.
4. **The answer is A** [II B]. This clinical scenario is that of a severe variable deceleration. As the umbilical cord is compressed, decreased perfusion of fetal tissue occurs. This causes the partial pressure of carbon dioxide to increase and the partial pressure of oxygen to decrease. The increased PCO_2 decreases the pH, resulting in acidemia. The initial event is therefore respiratory acidosis. When there is a prolonged decrease in perfusion, the fetus becomes dependent on anaerobic (not requiring oxygen) glycolysis to meet its energy return and thus produces pyruvic acid and lactic acid. This causes a further drop in the pH, resulting in metabolic acidosis. Eventually, if the acidosis is unresolved, asphyxia occurs. Uteroplacental insufficiency is a term that describes late decelerations. It does not describe the “acid–base” status of the fetus. Although increased PCO_2 (one of the initial occurrences) contributes to respiratory acidosis, it is not the best description of the fetal acid–base status.



Operative Obstetrics

THOMAS J. BADER

I

CESAREAN BIRTH

Cesarean section is delivery of a viable fetus through an abdominal incision (laparotomy) and uterine incision (hysterotomy). The first cesarean section was performed on a living patient in 1610. The maternal mortality rate was high up to the end of the 19th century, most often because of hemorrhage and infection. However, advances in surgical and anesthetic techniques, safe blood transfusions, and the discovery of effective antibiotics have led to a dramatic decline in the mortality rate.

A Incidence The incidence of cesarean sections in the United States has continued to increase over the past 30 years. Cesarean section is now the most common operative procedure performed in the United States.

1. In the United States, **approximately 32%** of infants were delivered by cesarean birth in 2007, compared to 21% in 1996, 15% in 1970, and 5% in 1960. Several factors contribute to the dramatic increase in cesarean births during this period.
 - a. As procedure-related morbidity and mortality rates decreased with advances in anesthetic and operative techniques, the rate of **primary cesarean sections** increased.
 - (1) The **widespread use of electronic fetal monitoring** has led to an increased rate of cesarean section for a nonreassuring fetal heart rate pattern.
 - (2) The **growing trend of delaying childbirth** in the United States has affected women in labor in two ways. First, a higher proportion of nulliparous women give birth. Second, nulliparity is associated with complications that increase rates of cesarean section, such as dystocia and preeclampsia. The average maternal age has increased in the past 20 years; rates of cesarean section increase with advancing age.
 - (3) **Dystocia** or abnormal progress of labor is used more freely as an indication for cesarean section, with a corresponding decline in the rate of forceps deliveries.
 - (4) Since a landmark article in 2000, vaginal **breech** deliveries are no longer recommended except in unusual circumstances. Virtually all babies with a breech presentation are now delivered by cesarean section.
 - (5) **Multiple gestations**, which are more commonly delivered via cesarean section, **occur more frequently** (likely due to assisted reproductive technologies).
 - b. As the number of primary cesarean sections increased, previous cesarean section as an indication for a **repeat cesarean section** increased. **Thirty-eight** percent of cesarean sections performed in the United States were repeat cesarean sections in 2004. There has also been diminished enthusiasm for attempts at vaginal birth after cesarean section (VBAC). In 2007, the VBAC rate in the United States had fallen to 8.5%.
2. **Perinatal mortality.** There is little documentation for an association between the increase in rates of cesarean delivery and a decline in perinatal mortality and morbidity. Although increasing rates of cesarean delivery initially led to decreased perinatal mortality, the perinatal mortality rate is not higher in European countries with lower cesarean birth rates. The major causes of perinatal morbidity and mortality continue to be low birth weight and congenital anomalies. In **preterm fetuses weighing greater than 750 g and with malpresentation**, however, cesarean section is believed to **improve** perinatal outcome.

B Indications Compared with vaginal delivery, a properly performed cesarean section carries no increased risk for the fetus; however, the risk of **maternal morbidity and mortality is higher**.

1. Contraindications to labor/indications for cesarean section

- a. Placenta previa
- b. Vasa previa
- c. Previous classic cesarean section
- d. Previous myomectomy with entrance into the uterine cavity
- e. Previous uterine reconstruction
- f. Malpresentations of the fetus
- g. Active genital herpes infection
- h. Previous cesarean section and patient declines trial of labor

2. Dystocia and failed induction of labor

- a. Cephalopelvic disproportion, failure to descend, or arrest of descent or dilation
- b. Failed forceps or vacuum extractor delivery
- c. Certain fetal malformations that may obstruct labor (i.e., large hydrocephalus, sacroccygeal tumor)

3. Emergent conditions that warrant immediate delivery

- a. Abruptio placentae with evidence of maternal or fetal compromise
- b. Umbilical cord prolapse
- c. Nonreassuring antepartum or intrapartum fetal testing
- d. Intrapartum fetal acidemia, with scalp pH of less than 7.20
- e. Uterine rupture
- f. Persistent bradycardia

C Types of cesarean operations Cesarean operations are classified according to the **orientation of the incision on the uterus (transverse or vertical)** and the **location of the incision on the uterus (lower segment or upper segment)**.

1. Low transverse. The low transverse uterine incision is the **preferred** incision and the one **most frequently used** today. The advantages of this incision are:

- a. The incision is made in the **noncontractile portion of the uterus**, minimizing chances of rupture or separation in subsequent pregnancies.
- b. The incision requires creation of a bladder flap and lies behind the peritoneal bladder reflection, which may reduce the risk of significant adhesion formation.
- c. **Uterine closure is accomplished more easily** because of the thin muscle wall of the lower segment, and the **potential for blood loss is lowest** with this type of incision.

A disadvantage of the low transverse incision is that it may involve potential extension into the uterine vessels laterally and into the cervix and vagina inferiorly.

2. Low vertical. The vertical incision begins in the noncontractile lower segment but usually extends into the contractile upper segment.

- a. This incision is used **when a transverse incision is not feasible**.
 - (1) The lower uterine segment may not be developed if labor has not occurred; the transverse incision may not provide enough room for delivery of the infant.
 - (2) Malpresentations of the term or premature infant may necessitate a vertical incision to allow more room for delivery of the infant.
 - (3) This incision is sometimes used when an anterior placenta previa is noted to facilitate delivery without cutting through the body of the placenta.
- b. This incision also requires creation of a bladder flap and allows for reperitonealization.
- c. The risk of **uterine rupture** in subsequent pregnancies **is increased** when the upper segment of the uterus is entered.
- d. **Uterine closure is more difficult**, and **blood loss is greater** if the upper segment is involved.

3. Classic incision (Sanger). The classic incision is a longitudinal incision in the anterior fundus.

- a. This incision is **currently used infrequently** because of the significant **risk of uterine rupture in subsequent pregnancies**, which can occur before labor begins, and higher complication rate.

- b. **Indications for this incision** include invasive carcinoma of the cervix, presence of lesions in the lower segment of the uterus (myomas) that prohibit adequate uterine closure, and transverse lie with the back down (most cases). It is the **simplest and quickest incision** to perform.
- c. This incision does not require bladder dissection, and reperitonealization is not performed; the potential for intraperitoneal adhesion formation is greater.
- d. **Uterine closure is more difficult** because of the thick muscular upper segment, and the **potential for blood loss is greater**.

D Procedure

1. Patient preparation

- a. **Informed consent** should always be obtained.
- b. The patient should be **well hydrated**.
- c. The **preoperative hematocrit** should be known, and a **blood type and screen** should be obtained. In certain clinical circumstances (e.g., placenta previa), blood should be readily available.
- d. The **bladder should be empty**. Placement of a Foley catheter is typical.
- e. **Prophylactic antibiotics** are usually given prior to skin incision (although antibiotics are sometimes held until after clamping of the umbilical cord).
- f. **Antacids** are also given to reduce the acidity of the stomach contents in the event that the patient aspirates material into the lungs.

- 2. **Anesthesia.** Most often, anesthesia is regional (spinal or epidural), but it can be inhalational (general) as dictated by the individual situation (see Chapter 13). General anesthesia may result in depression of the infant immediately after delivery, the degree of which increases with the length of time from incision to delivery. For this reason, the patient is prepared for incision *before* the induction of general anesthesia (i.e., Foley catheter placement, skin “prep,” and draping).

3. Surgical techniques

a. Abdominal incision

- (1) The abdominal incision is generally **midline** or **Pfannenstiel**.
 - (a) **Midline.** The infraumbilical vertical midline incision is less bloody and allows more rapid entry into the abdominal cavity.
 - (b) **Pfannenstiel.** This low transverse incision near the symphysis pubis provides the most desired cosmetic effect and is **used most often**. However, it generally requires more time to perform than a vertical midline.
- (2) The procedure is performed with the patient on the operating table in a **left lateral tilt** to prevent maternal hypotension and uteroplacental insufficiency, which may result from compression of the inferior vena cava by the uterus when the patient is supine.

- b. **Uterine incision.** The pregnant uterus is palpated and inspected for rotation. The type of uterine incision is selected depending on development of the lower uterine segment, presentation of the infant, and placental location.

- (1) A **bladder flap** is usually created to access the lower uterine segment. The reflection of bladder peritoneum is incised and dissected free from the anterior uterine wall, exposing the myometrium. This step is not essential with a classical incision.
- (2) **Incision of the myometrium** is made as indicated.

c. Delivery of the infant

- (1) The **infant** is delivered as a vertex or breech. A vacuum or even forceps are sometimes used to assist with delivery.
- (2) The **placenta** is delivered spontaneously or can be removed manually.

d. Wound closure

- (1) The **uterus is often exteriorized** onto the anterior abdominal wall to massage the fundus, inspect the adnexa, and facilitate visualization of the uterine incision for repair.
- (2) The **uterine cavity is cleaned** using a wet sponge over the gloved hand. Uterotonics are administered as indicated to facilitate contraction of the myometrium and promote hemostasis.
- (3) A **transverse uterine incision** is closed in one or two layers. A **vertical incision** usually is closed in two or three layers because of the myometrial thickness of the upper segment.

- (4) The **peritoneum of the bladder reflection** does not need to be closed and should be left open.
- (5) The **abdominal incision** is closed in the usual manner.

E Complications Common postoperative complications include the following conditions:

1. **Endomyometritis.** Postoperative infection is the most common complication after cesarean section.
 - a. Depending on the definition used, the **incidence of endomyometritis** after cesarean section may be as low as 5% or as high as 50%.
 - b. **Risk factors** include lower socioeconomic status, prolonged labor, prolonged duration of ruptured membranes, and the **number of vaginal examinations**.
 - c. Infection is **polymicrobial** and can include the following organisms: aerobic streptococci, anaerobic Gram-positive cocci, and aerobic and anaerobic Gram-negative bacilli.
 - d. Use of **prophylactic antibiotics** at the time of the procedure **decreases incidence** of endomyometritis. With the use of modern, broad-spectrum antibiotics, the incidence of serious complications, including sepsis, pelvic abscess, and septic thrombophlebitis, is less than 2%.
2. **Urinary tract infection**
 - a. Urinary tract infections are the **second most common infectious complication** following cesarean delivery after endomyometritis. Incidence varies from 2% to 16%.
 - b. **Practices that decrease risk** include strict adherence to aseptic technique during catheter placement and minimizing duration of catheter drainage of the bladder.
3. **Wound infection**
 - a. The **incidence** of postcesarean wound infection ranges from 2.5% to 16%.
 - b. **Risk factors** include prolonged labor, ruptured membranes, amnionitis, meconium staining, morbid obesity, anemia, and diabetes mellitus.
 - c. **Common isolates** include *Staphylococcus aureus*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides* sp., and group B *streptococci*.
4. **Thromboembolic disorders**
 - a. The **incidence** is 0.24% of deliveries, and deep vein thromboses are three to five times more common after cesarean delivery than vaginal delivery.
 - b. **Diagnosis and treatment** are the same as for nonpregnant women. Prompt diagnosis and treatment decrease the risk of complicating pulmonary embolus to 4.5% and that of death to 0.7%.
 - c. Because of the risk of thromboembolic events in pregnancy and following major surgery, women undergoing cesarean section should receive mechanical and/or pharmacologic **prophylaxis against deep venous thrombosis**.
5. **Cesarean hysterectomy**
 - a. Hysterectomy after cesarean delivery occurs in less than 1% of cesarean sections.
 - b. **Indications** include uterine atony (43%), placenta accreta (30%), uterine rupture (13%), extension of a low transverse incision (10%), leiomyoma preventing uterine closure, and cervical cancer.
6. **Uterine rupture in future pregnancies**
 - a. The **risk of rupture** of previous cesarean scar **varies with the location of the incision**.
 - (1) **Low transverse scar** (one): less than 1%
 - (2) **Low vertical scar**: 0.5% to 6.5%
 - (3) **Classic scar**: as high as 10%
 - b. Separation of the uterine scar can be categorized as **dehiscence or rupture**.
 - (1) A **dehiscence** is a frequently asymptomatic separation and is found incidentally at the time of repeat cesarean or on palpation after a vaginal birth. The muscle is disrupted, but the overlying peritoneum is intact (a “window”).
 - (2) **Uterine rupture** is a catastrophic event with sudden separation of the uterine scar and expulsion of the uterine contents into the abdominal cavity. Deterioration of the fetal heart rate tracing is usually the first sign of rupture, followed by severe abdominal pain and bleeding.

F Vaginal birth after cesarean section Since the 1980s, previous cesarean section has not been a contraindication to subsequent labor and a vaginal birth. All women who are candidates should be counseled adequately and offered an attempt at vaginal birth or a repeat cesarean section.

1. **Considerations.** The maternal risks of a VBAC, when performed in the proper setting, are less than the risks of a repeat cesarean section.
 - a. There is approximately a 60% rate of successful vaginal delivery after previous cesarean section.
 - (1) A previous vaginal delivery is the best prognostic indicator for success.
 - (2) Women with “nonrecurring” indications (e.g., breech presentation, nonreassuring fetal heart rate pattern, or hemorrhage) have higher success rates than women with “recurring” indications (e.g., previous cephalopelvic disproportion or failure to progress). However, as many as 50% of women with previous cesarean section for cephalopelvic disproportion have a successful vaginal birth.
2. **Prerequisites**
 - a. No maternal or fetal contraindications to labor
 - b. Previous low transverse or low vertical cesarean section, with documentation of the uterine scar
 - c. Informed consent regarding risks and benefits of repeat cesarean and vaginal birth
 - d. Personnel able to perform emergency delivery and appropriate facility
3. **Contraindications**
 - a. Previous classic uterine incision
 - b. Maternal or fetal contraindications to labor
 - c. Trial of labor declined by mother
 - d. The risk of VBAC in multiple gestations has not been determined

II

EPISIOTOMY

A Definition An episiotomy is an incision of the perineum made to enlarge the vaginal outlet to facilitate delivery.

1. It is made at the end of the second stage of labor just before delivery, when indicated.
2. It increases the area of the outlet for the fetal head during delivery, particularly in assisted deliveries with forceps or the vacuum extractor.

B Function

1. An episiotomy has been advocated in order to prevent major perineal lacerations, particularly at the time of operative vaginal delivery. However, there is no evidence to support this indication and there is evidence that episiotomy may be associated with an **increased risk** of lacerations of the anal sphincter or rectum.
2. Prophylactic episiotomy has been advocated to prevent pelvic relaxation, although this too has never been demonstrated.
3. Episiotomy has also been used in an effort to shorten the second stage of labor or effect rapid delivery if there is evidence of fetal compromise. There is no evidence supporting this application.
4. **Given the absence of clear evidence of benefit it is recommended that episiotomy NOT be performed routinely and only be used in selected cases.**

C Types

1. **Median or medial episiotomy.** This incision is cut vertically in the midline of the perineal body.
 - a. **Advantages:** less blood loss, easier to repair, more comfortable during healing
 - b. **Disadvantage:** possible occurrence of inadvertent incision or extension into the anal sphincter and rectum. It is important to recognize and repair this complication during repair of the episiotomy to prevent rectovaginal fistula
2. **Mediolateral episiotomy.** This incision is made at a 45-degree angle to the hymenal ring; it extends lateral and posterior.
 - a. **Advantage:** more room with less risk of injury to the rectum and sphincter
 - b. **Disadvantages:** more difficult to repair, more blood loss, more discomfort during healing

III

OPERATIVE VAGINAL DELIVERY: FORCEPS AND VACUUM EXTRACTOR

- A Definition** An operative vaginal delivery is defined as the application of direct traction on the fetal head with forceps or a vacuum.
- B Incidence** The incidence of operative vaginal delivery is approximately 5% to 10% of vaginal deliveries.
- C Indications** An operative vaginal delivery is performed to shorten the second stage of labor with certain maternal or fetal indications.
- 1. Nonreassuring fetal status** based on heart rate pattern, auscultation, lack of response to scalp stimulation, or scalp pH
 - 2. Prolonged second stage of labor** secondary to malposition, deflexion, or asynclitism (lateral deflection) of the fetal head. A prolonged second stage is defined as follows:
 - a. Nulliparous patient:** more than 3 hours with a regional anesthetic or more than 2 hours without regional anesthesia
 - b. Multiparous patient:** more than 2 hours with a regional anesthetic or more than 1 hour without regional anesthesia
 - 3. Certain maternal illnesses** (such as heart disease or pulmonary compromise), which make avoidance of voluntary maternal expulsive efforts (i.e., valsalva) desirable
 - 4. Poor voluntary expulsion efforts** because of exhaustion, analgesia, or neuromuscular disease
- D Prerequisites for instrumental delivery**
1. The cervix must be fully dilated.
 2. The membranes must be ruptured.
 3. The position and station must be known, and the head must be engaged (0 station; see Chapter 10).
 4. The maternal pelvis must be judged adequate in size for delivery.
 5. The bladder should be empty.
 6. A skilled operator must be present.
 7. Adequate anesthesia is needed before forceps or vacuum application.
- E Contraindications**
1. Nonvertex presentation (except for Piper forceps in the breech delivery)
 2. **Nonengagement** of the presenting part
 3. Head that cannot be advanced with ordinary traction when using forceps or the vacuum extractor
 4. Prematurity, fetal bleeding disorder, or certain maternal infections (i.e., HIV)
- F Classification of forceps deliveries** Forceps deliveries are classified according to station and rotation (Fig. 12–1).
- 1. Outlet forceps.** To be categorized as an outlet forceps delivery, the following criteria must be satisfied:
 - a.** Scalp is visible at the introitus without separating the labia.
 - b.** Fetal skull has reached the pelvic floor.
 - c.** Sagittal suture is in the anteroposterior diameter or right or left occiput anterior or posterior position.
 - d.** Fetal head is at or on the perineum.
 - e.** Rotation does not exceed 45 degrees.
 - 2. Low forceps.** In a low forceps delivery, the leading point of the fetal skull has descended to at least +2 station (out of 5), but has not reached the pelvic floor.
 - 3. Midforceps.** The station is above +2 but the presenting part is engaged.
 - 4. High forceps.** High forceps procedures are no longer performed.

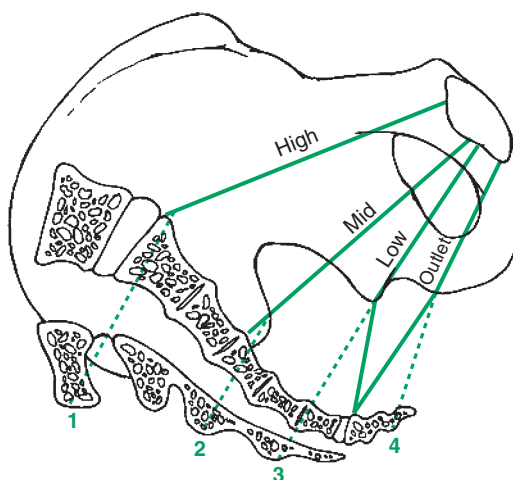


FIGURE 12-1 The four major planes of the pelvis.

G Types of forceps The forceps are two matched blades that articulate and lock. The design of the blades provides standard cephalic and pelvic curves; that is, they conform to the shape of the fetal head and to the vaginal canal, respectively. Each matching part of the forceps has three parts: the blade, the shank, and the handle.

1. **Classic.** These forceps are used primarily for traction when there is to be little or no rotation (Fig. 12-2).
2. **Specialized.** These forceps are designed for rotation or special indications (Fig. 12-3).
 - a. **Kielland** (for rotation)
 - b. **Barton** (for rotation)
 - c. **Piper** (for the aftercoming head in breech deliveries)

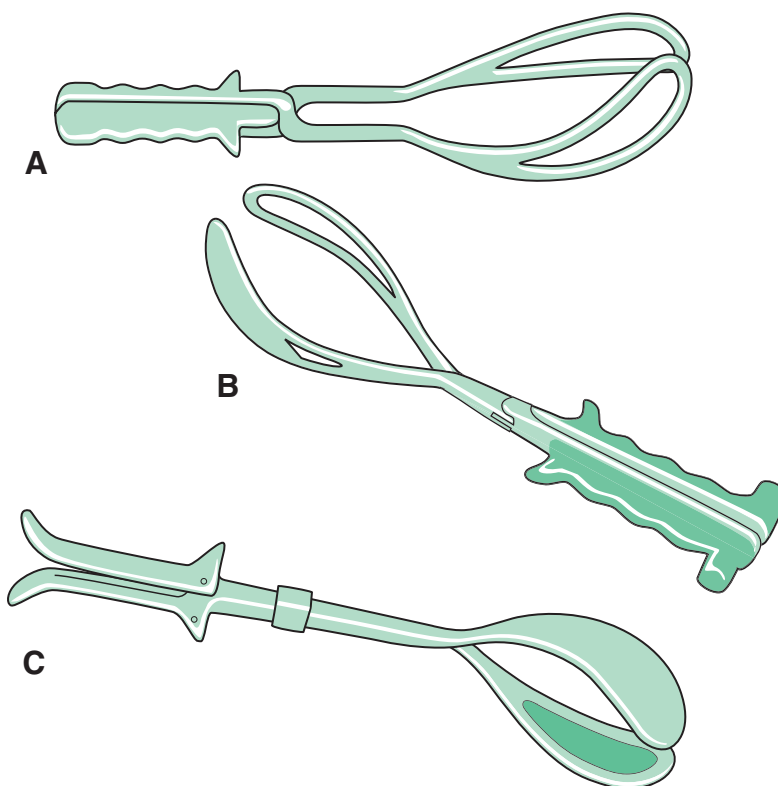


FIGURE 12-2 Classic forceps: **A.** Simpson. **B.** Elliot. **C.** Tucker-McLean.

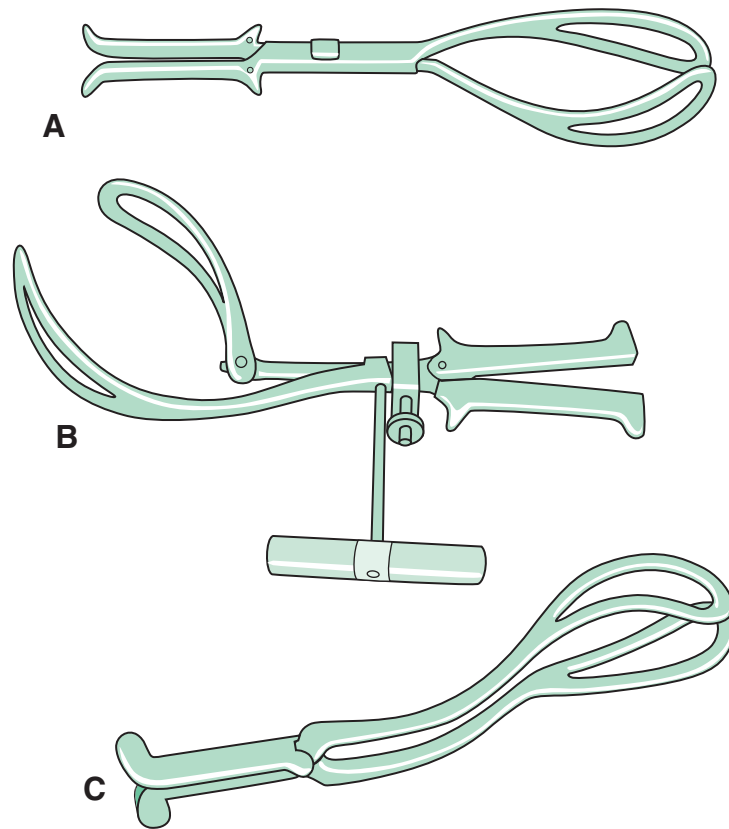


FIGURE 12-3 Specialized forceps: **A.** Kielland (for rotation). **B.** Barton (for rotation). **C.** Piper (for the aftercoming head in breech deliveries).

H Vacuum extractors There are two types of vacuum extractors, based on the type of cup used for application to the fetal head. Each type has three parts: a cup, a hose, and a vacuum device.

1. **Malmström vacuum extractor.** This device consists of a metal cup (40 to 60 mm in diameter) that is applied to the fetal scalp. The pump is then used to create a vacuum. Traction is then applied to bring the infant's head through the introitus.
2. **Plastic cup extractor.** This device, which is **more widely used in the United States**, consists of a flexible silastic cup that is applied to the fetal head.

I Complications

1. **Maternal complications** include lacerations of the cervix, vagina, and perineum; episiotomy extensions; and associated hemorrhage. These occur in up to 22% of women undergoing forceps deliveries. More serious complications (incidence, 0.1% to 0.3%) include bladder lacerations, pelvic floor injury, pelvic hematoma, and coccygeal fracture.
2. **Neonatal injury**
 - a. **Scalp abrasions or lacerations** are the most common injury associated with vacuum extraction.
 - b. **Soft tissue injury** is the most common injury associated with **forceps delivery**.
 - c. **Cephalohematoma** (separation of the fetal scalp from underlying structures) occurs in 0.5% to 2.5% of live births, with an incidence of 14% to 16% in vacuum deliveries and 2% in forceps deliveries.
 - d. **Subgaleal hemorrhages** occur in 26 to 45 in 1,000 vacuum deliveries.
 - e. **Intracranial hemorrhage** is a rare complication, occurring in 0.75% of instrumental deliveries.
 - f. **Facial nerve injuries** can occur with forceps. They are almost always transient.

IV

CERVICAL CERCLAGE

A Definition A suture is placed in the cervix to treat **cervical insufficiency**.

1. Cervical insufficiency is **characterized** by gradual, progressive, painless dilation of the cervix, usually leading to spontaneous pregnancy loss in the **second trimester**. Although the incidence is difficult to determine due to imprecise definitions, it is thought that only a minority of the second-trimester losses are due to cervical insufficiency.
2. Cervical insufficiency may be **acquired or congenital**.
 - a. **Acquired causes** primarily result from obstetric or gynecologic trauma to the cervix (e.g., surgical dilation, cone biopsy or LEEP of the cervix).
 - b. **Congenital causes** may include Mullerian anomalies or exposure to diethylstilbestrol exposure in utero.
3. There is an ongoing debate about the potential benefit of universal or targeted ultrasound screening for cervical length and the subsequent use of cerclage for those women found to have a shortened cervix. There is evidence suggesting a decreased rate of the *third-trimester* preterm delivery with this approach.

B Techniques Cervical cerclage involves placing an encircling suture around the **cervical os** using a heavy, nonabsorbable suture or Mersilene tape. The mechanism by which cerclage is effective is poorly understood. **Three techniques** for cervical cerclage are used today.

1. **Shirodkar technique.** In the more complicated of the two vaginal procedures, the suture is almost completely buried beneath the vaginal mucosa at the level of the internal os. It can be left in place for subsequent pregnancies if a cesarean section is performed. This procedure requires dissection of the bladder and is associated with an increased blood loss compared with a McDonald cerclage.
2. **McDonald technique.** This procedure is a simple purse-string suture of the cervix. It involves less trauma to the cervix and less blood loss than the Shirodkar procedure (Fig. 12–4).

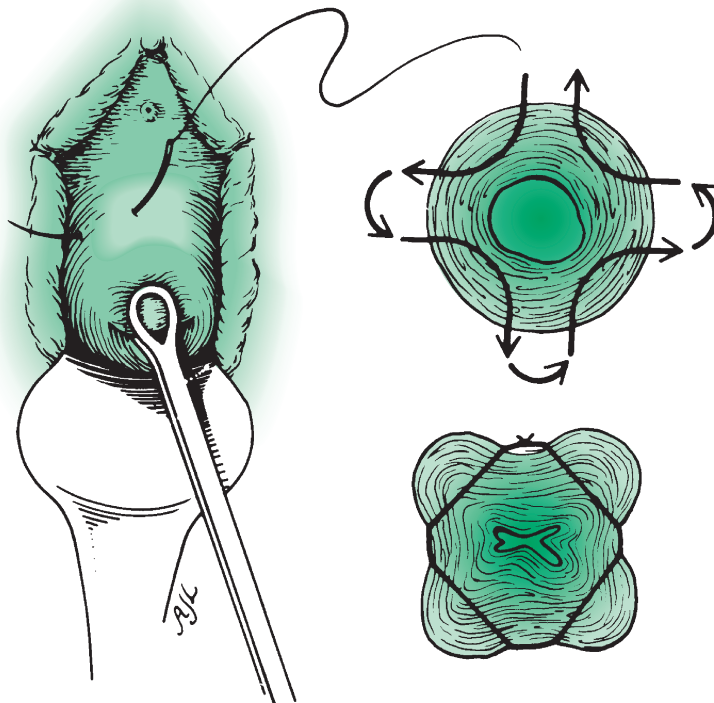


FIGURE 12–4 McDonald cerclage.

3. Abdominal placement. This is an uncommon, semipermanent procedure used in women with a short or amputated cervix or in those in whom a vaginal cerclage has failed. Cesarean birth is necessary for delivery.

C Timing Cerclage is **usually performed** between the **12 and 16** weeks of gestation but can be performed as late as the 24 weeks of gestation. **Fetal viability and the absence of anomalies** should be documented **before** performing the procedure. The suture is generally **removed at the 37 weeks' gestation** or earlier if labor begins.

D Effectiveness The **success rate of cerclage** varies tremendously on the basis of the population and the inclusion criteria. The best data on the efficacy of cerclage show a benefit only for those women with the worst pregnancy history (i.e., three or more second-trimester losses). Except in women with a strong history consistent with cervical insufficiency, the benefit of cerclage has not been proven.

E Complications

1. Cervical lacerations occur in 1% to 13% of deliveries after a McDonald cerclage.
2. Cervical dystocia with failure to dilate, requiring a cesarean birth, occurs in 2% to 5% of cases.
3. Displacement of the suture occurs in 3% to 12% of cases. A second cerclage may then be attempted.
4. Premature rupture of the membranes complicates cerclage in 1% to 9% of cases.
5. Chorioamnionitis complicates 1% to 7% of cases.
6. Early, elective cerclages have a low rate (1%) of infection; cerclage placement with dilation of the cervix has a much higher risk (30%) of infection.

V

ABORTION

The end of a pregnancy before viability (usually considered to be 24 weeks' gestation) is known as an abortion. Abortions can occur spontaneously or intentionally (i.e., induced).

A Spontaneous abortion is expulsion of the products of conception without medical or mechanical intervention.

1. **Incidence.** Spontaneous loss occurs in at least 15% of clinically recognized pregnancies; the risk increases directly with maternal age, advancing paternal age, minority race, increasing gravidity, and history of previous spontaneous losses.
2. **Etiology.** Chromosomal abnormalities are the most common reason for the first-trimester losses, occurring at a 60% frequency. Most chromosomal abnormalities are sporadic defects; in a small percentage of cases, one of the parents carries a balanced translocation. Autosomal trisomies are the most common anomaly, followed by 45,X0 monosomy (the most common single anomaly seen in abortuses), triploidy, tetraploidy, translocations, and mosaicism.
3. **Classification.** Spontaneous abortions are classified into four types.
 - a. **Inevitable abortion:** This includes bleeding, cramping, or rupture of the membranes associated with dilation of the cervix. In this circumstance, the loss of the pregnancy is "inevitable." Management generally consists of medical or surgical emptying of the uterus to complete the abortion.
 - b. **Incomplete abortion.** This type of pregnancy loss occurs when there has been partial but incomplete expulsion of the products of conception from the uterine cavity. Depending on the clinical circumstances and patient preference, management can be expectant (with eventual spontaneous passage of remaining tissue) or the woman can undergo medical or surgical emptying of the uterus.
 - c. **Complete abortion.** This occurs when a previously diagnosed intrauterine pregnancy is completely expelled from the uterus. No medical intervention is necessary.
 - d. **Missed abortion.** Death of the fetus or embryo may occur without the onset of labor or the passage of tissue for a prolonged period. Again, depending on the clinical circumstances and the woman's preference, management can be expectant (with the first-trimester losses) or medical or surgical intervention to empty the uterine contents.

B Induced (elective) abortion Abortion became legal in 1973 and can be performed up to approximately 24 weeks' gestation in most states. Legal abortion is one of the most frequently performed surgical procedures in the United States. Therapeutic abortions are terminations of pregnancy that are performed when maternal risk is associated with continuation of the pregnancy or fetal abnormalities are associated with genetic, chromosomal, or structural defects.

1. Techniques of pregnancy termination. Techniques used effectively to empty the uterus of the products of conception fall under the categories of surgical evacuation or medical management. The preferred procedure depends on gestational age and operator training.

a. Surgical evacuation

(1) **Suction curettage.** This method of dilation of the cervix and vacuum aspiration of the uterine contents is used for termination of pregnancy up to 14 weeks' gestation. Suction curettage is the most common method of pregnancy termination in this country.

(a) **Hygroscopic dilators** such as laminaria (stems of a brown seaweed that absorb water) can be used when necessary to facilitate gentle dilation of the cervix 12 to 24 hours prior to the procedure.

(b) Prostaglandin (misoprostol) given vaginally or orally can also soften and dilate the cervix as an adjunct to suction curettage.

(c) **Prophylactic antibiotics** administered just before or after the procedure significantly reduce the risk of infection associated with induced abortion.

(2) **Dilation and extraction (D&E).** This technique is the preferred method of termination at 13 or more weeks of gestation.

(a) Wider cervical dilation is necessary to accomplish uterine evacuation in the second trimester. Preoperative osmotic (e.g., laminaria) and/or pharmacologic (e.g., misoprostol) agents are used to prepare the cervix.

(b) **Evacuation of the uterus** is accomplished through a combination of vacuum aspiration and forcep extraction of fetal parts. A final sharp curettage may also be performed in an effort to ensure complete emptying of the uterus. Evaluation to ensure removal of major fetal parts is an important component of this procedure. Simultaneous ultrasound monitoring can be helpful to decrease risk to the mother and ensure complete evacuation of the uterus.

(c) Prophylactic **antibiotics** may be given.

b. Induction of labor. Medical means of inducing abortion include extrauterine and intrauterine administration of abortifacients, such as prostaglandins, hypertonic saline, and oxytocin. These methods are used for the second-trimester terminations.

(1) **Prostaglandins** are most commonly administered as vaginal tablets of prostaglandin E₂; 90% of abortions are accomplished within 24 hours. Common side effects include fever, nausea and vomiting, diarrhea, and uterine hyperstimulation.

(2) **Hypertonic solutions of saline** can be injected directly into the amniotic cavity. This procedure requires amniocentesis and care to avoid intravascular injection.

(3) **Hi-dose oxytocin** can be used to induce labor in the late second trimester.

(4) Complication rates are lowest when the uterus is successfully evacuated within 13 to 24 hours. Laminaria to facilitate cervical dilation is useful to shorten the length of induction.

c. Medical abortion

(1) **Misoprostol** is an analog of prostaglandin E₁. By interacting with prostaglandin receptors, misoprostol causes the cervix to soften and the uterus to contract, resulting in the expulsion of the uterine contents. Dosage of 800 µg given once intravaginally. A second dose can be administered 24 hours later. Because of severe cramping, it is usually given with pain medication (narcotic) and antiemetics. The success rate is 75% to 85% when administered in the first 9 weeks of pregnancy.

(2) **Mifepristone**, a progesterone antagonist is used to effect termination of pregnancies up to 7 weeks' gestation. Abdominal and uterine cramping are common. Major complications (e.g., hemorrhage, retained tissue, significant infection) are rare and likely comparable to the rate associated with surgical termination. Effectiveness is improved when mifepristone is given in combination with misoprostol to promote uterine evacuation.

(3) **Methotrexate** (in combination with misoprostol) has also been used to perform medical abortions.

2. **Anesthesia.** Sedation with a local paracervical block is usually used for induced abortion. General anesthesia can be used but is accompanied by a higher incidence of hemorrhage, cervical injury, and perforation because general anesthetics render the uterine musculature more relaxed and, thus, easier to penetrate.
3. **Complications.** The incidence of complications is largely determined by the method of termination and gestational age; incidence varies directly with increasing gestational age.
 - a. **Immediate complications.** These complications develop during the procedure or within 3 hours after completion.
 - (1) **Hemorrhage.** The incidence of hemorrhage is most accurately determined by the rate of transfusion. Rates vary with method of termination and are reported to be from 0.06% to 1.72%. The lowest rates are seen with suction curettage, and the highest with saline instillation.
 - (2) **Cervical injury.** The rates of cervical injury associated with suction curettage are within the range of 0.01% to 1.6%. Factors that decrease the risk of this complication include the use of local anesthetics instead of general anesthesia; use of laminaria; and an experienced operator.
 - (3) **Uterine perforation.** The incidence of this potentially serious complication of suction curettage abortions is approximately 0.2%.
 - (a) **Risks.** Factors that increase the risk of uterine perforation include multiparity, advanced gestational age, and operator inexperience. The use of laminaria to facilitate cervical dilation decreases the risk.
 - (b) **Complications.** Serious consequences of uterine perforation include hemorrhage and damage to intraabdominal organs. Because of the location of the uterine vessels, lateral perforations may be associated with hemorrhage.
 - (c) **Treatment.** Many cases of uterine perforation require only observation. Surgical exploration is indicated when there is evidence of hemorrhage, when injury to abdominal organs is suspected, or when perforation occurs with a suction curette.
 - (4) **Acute hematometra.** This complication occurs in 0.1% to 1% of suction curettage procedures and is evidenced by decreased vaginal bleeding and an enlarged, tender uterus. **Treatment** is repeat curettage and administration of an oxytocic agent.
 - b. **Delayed complications**
 - (1) **Postabortal infection.** This condition is often associated with retained tissue. The incidence of infection varies with the method of termination.
 - (a) **Risks.** Factors that increase the risk of infection include the presence of cervical gonococcal or chlamydial infection, advanced gestational age, uterine instillation methods of termination, and the use of local anesthesia instead of general anesthesia. Infection complicates less than 1% of suction curettage procedures, 1.5% of D&E terminations, and 5.3% to 6.2% of induction terminations.
 - (b) **Treatment.** Uterine infection is usually polymicrobial, similar to other gynecologic infections, and is treated with broad-spectrum antibiotics and prompt evacuation of retained tissue. The use of prophylactic antibiotics significantly decreases the risk of infectious complications associated with induced abortions.
 - (2) **Retained tissue.** This condition complicates less than 1% of suction curettage abortions.
 - (a) **Associated conditions.** Retained tissue may be associated with infection, hemorrhage, or both.
 - (b) **Treatment.** Therapy requires repeat curettage and antibiotic administration if infection is present.
 - (3) **Rh sensitization.** The risk of sensitization increases with advanced gestational age. The Rh status of every pregnant woman should be known, and Rh immune globulin (RhoGAM) should be administered to an Rh-negative woman whenever maternal fetal to maternal hemorrhage is a possibility (such as with a spontaneous or induced abortion).
 - (a) The estimated risk of sensitization associated with suction curettage is 1.8%, if RhoGAM is *not* administered appropriately.
 - (b) The recommended dose for Rh immune globulin prophylaxis is 50 μ g up to 12 weeks' gestation, and 300 μ g thereafter.

- (4) **Future adverse pregnancy outcomes.** The incidences of infertility, spontaneous abortion, and ectopic pregnancy **do not** increase after uncomplicated suction curettage procedures.
- (5) **Asherman's syndrome** is defined as intrauterine adhesions (or synechiae). These adhesions can be present anywhere in the uterine cavity and can affect a portion of the cavity or can obliterate the whole cavity. Those adhesions that obstruct the outflow tract present as amenorrhea with associated menstrual cramping. This condition can occur after D&C or D&E for pregnancy-related conditions such as missed abortion, incomplete abortion, especially with concurrent infection, and following D&C for postpartum hemorrhage or retained products. Treatment is surgical excision of the adhesions by hysteroscopy to restore the uterine cavity to normal. With extensive adhesions, the procedure may need to be performed several times.

4. **Maternal mortality.** The case mortality rate for induced abortion is less than 1 per 100,000 procedures. The risk varies with gestational age and method of termination.
 - a. The leading cause of death associated with induced abortion is anesthetic complications, followed (in frequency) by hemorrhage, embolism, and infection.
 - b. The risk of death is lowest for suction curettage procedures and highest for instillation procedures. Risk increases with advancing gestational age.

C Threatened abortion This includes bleeding or cramping occurring in the first-half of gestation without cervical dilation or passage of tissue and with confirmed embryonic/fetal viability. Twenty-five percent of pregnant women experience spotting or bleeding early in gestation; 50% of these proceed to lose the pregnancy. Management is generally expectant. Some providers advocate bed rest and pelvic rest.

D Recurrent pregnancy loss (see Chapter 31). In the past, this condition has been called **habitual abortion or recurrent miscarriage** and is defined as three or more spontaneous, consecutive first-trimester losses. This affects 2% of couples. In women with previous liveborn infants who have had a loss, the risk of a subsequent abortion is 25% to 30% regardless of whether she has had one or more losses. In women with no previous liveborn infants, the recurrence risk is 40% to 45%. Evaluation is indicated after three losses (and sometimes after two losses depending on the age of the woman).

1. **Workup for recurrent pregnancy loss.** There are many tests which have been recommended in the evaluation of women who have experienced three or more pregnancy losses. However, there are relatively few tests where there is evidence showing (1) a clear association with recurrent loss and (2) an effective intervention to improve outcomes. The humane desire to “do something” or to explain this unfortunate condition should not lead to unnecessary testing and treatment. The following assessments should be performed and this evaluation can lead to interventions that increase the likelihood of a successful pregnancy in the future.
 - a. Detailed history and physical examination to identify maternal illness
 - b. Chromosomal evaluation of the couple
 - c. Thyroid function test
 - d. Hysterosalpingogram, sonohysterogram, or hysteroscopy to evaluate the uterine cavity
 - e. Screening test for lupus anticoagulant and anticardiolipin antibody



Study Questions for Chapter 12

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A 26-year-old woman, gravida 2, para 1, at 20 weeks of gestation, sees you in the office for prenatal care. Her fundus measures 18 cm and you are unable to hear fetal heart tone by Doppler. You perform an ultrasound and confirm lack of fetal heart activity and lack of fetal movement. She has had no bleeding or cramping. Which of the following is the most descriptive diagnosis?

- ☐ A Threatened abortion
- ☐ B Complete abortion
- ☐ C Incomplete abortion
- ☐ D Spontaneous abortion
- ☐ E Missed abortion

2. A 36-year-old female has been in labor for over 12 hours. She has been pushing for 2 hours and on examination the fetal head is determined to be occiput anterior with a cervical examination of complete dilatation, 100% effaced and +2 station. You have elected to perform an operative vaginal delivery as the fetal tracing is becoming less reassuring. Which one of the following statements are true?

- ☐ A Cephalohematoma is more common with forceps delivery than vacuum delivery
- ☐ B The Malmstrom vacuum extractor is a flexible silastic cup and is more widely used in the United States
- ☐ C This would be classified as a midforcep delivery
- ☐ D Scalp abrasions or lacerations are the most common injury associated with vacuum delivery
- ☐ E Cervical and vaginal lacerations following operative vaginal delivery has an incidence of less than 1%

3. A 30-year-old woman, gravida 4, para 3, at 12 weeks of gestation, is seeing you for prenatal care. Her first pregnancy ended with a successful vaginal delivery, at term. Her second pregnancy was uncomplicated and resulted in a cesarean section with low transverse incision of uterus for breech presentation. She plans no further children after this pregnancy. What is the best advice you can give this patient regarding VBAC?

- ☐ A You are not a candidate for VBAC
- ☐ B You are a better than average candidate for VBAC
- ☐ C You are an average candidate for VBAC
- ☐ D You should proceed with scheduled repeat cesarean section and tubal ligation
- ☐ E Your risk of uterine rupture is 1 in 60

4. You are monitoring the progress of a woman (gravida 2, para 0) who has been in labor for the past 24 hours; her membranes have been ruptured for 17 hours. Three hours ago, her cervix was 10 cm dilated and 100% effaced. The fetal vertex had reached the pelvic floor and was in the left occiput anterior position. She has an epidural. The fetal heart rate tracing was reassuring, and she began pushing. Now, the fetal vertex has reached +2 station though the fetal vertex feels asynclitic. Which one of the following is true?

- ☐ A Vacuum delivery can be performed with a cervix that is not fully dilated whereas use of forceps requires the cervix be fully dilated
- ☐ B Operative vaginal delivery was indicated 1 hour ago in this patient when she had been pushing for 2 hours as she is gravida 2
- ☐ C Head position is not important for vacuum delivery
- ☐ D Emptying the bladder is not necessary as it would increase the risk of a urinary tract infection (UTI)
- ☐ E Adequate anesthesia is required for both forceps and vacuum delivery

QUESTIONS 5–9

Match the description below with the best range of numbers above. Each answer choice may be used once, more than once, or not at all.

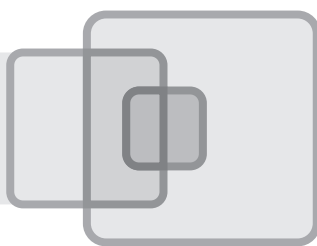
- A** 0% to 10%
- B** 25% to 30%
- C** 35% to 45%
- D** 60% to 70%
- E** 71% to 80%

5. Risk of sensitization in Rh-negative woman after D&E if RhoGAM not given
6. Risk of uterine perforation after D&E
7. After three spontaneous abortions (SABs), risk of SAB if no history of liveborn
8. Annual percent of births by cesarean section in the United States
9. Success rate for VBAC after one previous low transverse cesarean section for fetal distress and two previous successful VBACs



Answers and Explanations

1. **The answer is E** [V A 3 d]. The best term to describe this clinical scenario is “missed” abortion. Death of the fetus or embryo (less than 23 weeks and before viability) occurred without onset of labor or passage of tissue and was unrecognized for 4 weeks. A threatened abortion is an event that is occurring in the present. The fetus is alive inside the uterus but is threatening to abort. A complete abortion would not demonstrate any fetal tissue on ultrasound. An incomplete abortion describes an abortion in progress. This means that the patient recently had bleeding and cramping, and there was partial or incomplete expulsion of the products of conception. A spontaneous abortion is too broad a term. Most of the answer choices are subtypes of “spontaneous abortion.”
2. **The answer is D** [III F–I]. Scalp abrasions or lacerations are the most common injury associated with vacuum delivery, while soft tissue injury is the most common neonatal injury with forceps. The Malmstrom vacuum extractor is a metal cup, not a flexible silastic cup. The silastic cup is used more commonly in the United States. This would be considered a low forceps delivery as the station is 2+. For this to be a midforceps delivery the station would need to be above 2+. The incidence of minor maternal complication of operative vaginal delivery, such as cervical and vaginal lacerations is 1.4% to 22%.
3. **The answer is B** [I F 1 a (2)]. This patient is an excellent candidate for VBAC for two reasons: she has had one prior successful VBAC with her third pregnancy and she had a cesarean section with her second pregnancy for a “nonrecurring” reason (breech). The decision to not have any further pregnancies should not dictate the route of delivery. The risk of uterine rupture after one previous low transverse type of cesarean section is less than 1% (i.e., less than 1 in 100).
4. **The answer is D** [III C, D]. This clinical scenario describes the protracted second stage of labor with regional anesthesia in a primipara, which is an indication for assisted vaginal delivery if the appropriate criteria are met. This patient has had two pregnancies, but she is a primipara, and she has regional anesthesia, therefore operative vaginal delivery is appropriate after 3 hours of pushing. If she had not had regional anesthesia, then operative delivery could be considered after 2 hours. Head position is important when considering both forceps and vacuum extraction. Adequate anesthesia always needs to be assured prior to operative vaginal delivery and, likewise the patient’s bladder needs to be emptied as a full bladder can obstruct descent of the head and progression through the pelvis.
5. **A** [V B 3 b (3)], **6. A** [V B 3 a (3)], **7. C** [V D], **8. B** [I A 1], **9. E** [I F 1 a]. The estimated risk of sensitization (i.e., formation of antibodies against the Rh antigen on red blood cells) associated with curettage is 1.8%, if RhoGAM is not administered. The incidence of uterine perforation after a suction curettage is 0.2%. After three spontaneous abortions, a woman with a previous liveborn infant has a 25% to 35% risk of SAB versus 40% to 45% with no history of any liveborn. Approximately, 32% of infants were delivered by cesarean birth in 2007. There is a 60% to 80% rate of successful vaginal delivery after previous cesarean section, especially if there is a nonrecurring indication (fetal distress) and previous successful VBAC.



Obstetric Anesthesia

ROBERT GAISER

I

INTRODUCTION

- A** Obstetric anesthesia involves caring for the parturient and her fetus. The major objectives for the obstetric anesthesiologist include:
1. Pain control during labor and delivery that is safe for both mother and fetus.
 2. Anesthetic management during cesarean delivery that does not result in a depressed neonate or in harm to the mother.
 3. Assisting the obstetrician with the blood pressure and heart rate of complicated parturients and with the management of comorbidities during labor.
- B** All large hospitals provide 24-hour anesthesia coverage of the labor and delivery suite. The last examination of the obstetric anesthesia workforce in 1992 revealed that obstetric anesthesia was available in 80% of hospitals with a delivery rate of 500 deliveries per year. Also, the number of hospitals maintaining an obstetric service if the delivery rate is less than 500 deliveries per year is decreasing. In the United States, approximately 95% of parturients receive some form of analgesia or anesthesia during childbirth.
- C** Two terms are important to understand. Analgesia refers to pain relief; it does not involve the removal of complete sensation. Anesthesia refers to rendering the patient completely insensate to pain. While analgesia is typically achieved with regional anesthesia (epidural or spinal), anesthesia is accomplished via two means:
1. General anesthesia involves the administration of intravenous and inhaled agents to render the patient unconscious; the entire body is rendered insensate. During general anesthesia, the patient is at risk for aspiration if an endotracheal tube is not in place. Management of the airway is the primary cause of mortality from general anesthesia.
 2. Regional anesthesia involves the administration of local anesthetic to render a specific part of the body insensate to surgery. For obstetrics, regional anesthesia consists of spinal and epidural anesthesia. Since the parturient maintains her natural airway, aspiration is not a concern. The major cause of morbidity from regional anesthesia is an excessive level, requiring management of ventilation and of hemodynamics.
- D** Obstetric anesthesia, while safer today than 20 years ago, continues to account for cases of maternal mortality. In the United Kingdom, the longest running quality assurance program (Confidential Enquiries into Maternal Mortality) exists for maternal mortality. In the most recent time period, 2002 to 2005, anesthesia ranked seventh among the causes. In the United States, while mortality has decreased, there has recently been an increase in death from meningitis (related to spinal anesthesia) and hypoventilation postoperatively following general anesthesia.
- E** Obstetric anesthesia involves the care of two patients, the mother and fetus. The mother undergoes various physiologic changes to adapt to the enlarging uterus and to support the growing fetus. These changes must be considered when designing a plan for the patient's analgesia.

II**PHYSIOLOGIC CHANGES OF PREGNANCY****A Cardiac**

1. Pregnancy results in an increase in cardiac output to meet the demands of increased oxygen consumption. Cardiac output increases 40% during pregnancy, with most of the increase occurring during the first trimester. The increase in cardiac output allows a 10- to 20-fold increase in uterine blood flow (from 50 mL/min in nonpregnant state to 500 to 700 mL/min at term). The increase in cardiac output is multifactorial, resulting from an increase in both stroke volume and heart rate (an increase of 10 to 20 beats/min [bpm]). Despite the increase in cardiac output, systolic, diastolic, and mean blood pressure decrease (Table 13–1).
2. Maternal blood volume increases during pregnancy by 35%. The increase begins early in gestation and continues throughout pregnancy. The increased blood volume during pregnancy allows parturients to tolerate normal blood loss of delivery (approximately 400 mL during vaginal delivery and 700 mL during cesarean section). Blood volume returns to prepregnancy levels within 7 to 14 days after delivery.
3. Normal parturients are less responsive to vasopressors and chronotropic agents, such as ephedrine and phenylephrine or ephedrine. This decrease in response may be related to downregulation of α and β receptors. As such, one may need to increase the amount of vasopressor administered to a pregnant patient.
4. Both phenylephrine and ephedrine improve uterine blood flow in hypotensive parturients. Phenylephrine results in higher umbilical cord pH as ephedrine crosses the placenta and stimulates the fetal sympathetic system, resulting in increased oxygen consumption with lactic acidosis.
5. In the supine position, up to 15% of pregnant patients develop nausea, hypotension, and vomiting (supine hypotension syndrome). The supine position allows the gravid uterus to compress the inferior vena cava and aorta. Compression of the vena cava results in decreased venous return to the right atrium and subsequent decreased cardiac output. This decrease in venous return may be compensated by the sympathetic nervous system. Anesthetic drugs and techniques blunt the sympathetic response and prevent compensation. A decrease in blood pressure results in a decrease in uterine perfusion. Further decreases in uterine blood flow occur if the uterus compresses the aorta. By tilting the patient to the left, the uterus is displaced off the vena cava and aorta. As such, pregnant women should not lie supine after 20 weeks' gestation, especially if they have received anesthesia. The uterus should be tilted to the left by placing a wedge underneath the right hip (Fig. 13–1).

B Respiratory system

1. Various changes occur in the maternal airway during gestation. There is vascular engorgement of the airway, resulting in possible edema of the oral and nasal pharynx, larynx, and trachea. This airway edema may render intubation of the trachea difficult. Exacerbation of these changes may occur in patients with upper respiratory tract infections or preeclampsia. The mucous membranes are also very friable. Manipulation, such as nasal intubation or the insertion of a nasogastric tube, may result in excessive bleeding.
2. The gravid uterus results in a 4-cm elevation of the diaphragm. Despite this elevation, there is little change in total lung capacity as the chest expands in the anterior–posterior and transverse diameter to compensate. The diaphragmatic elevation does cause a 20% decrease in functional residual

TABLE 13–1 Changes in Cardiac Output During Pregnancy

Gestational Age	Increase in Cardiac Output Over Baseline (%)
First trimester	40
Second trimester	50
Latent phase labor	65
Active phase labor	80
Immediately postpartum	130

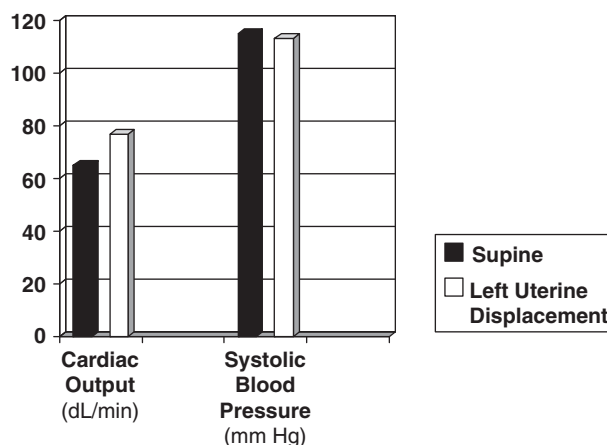
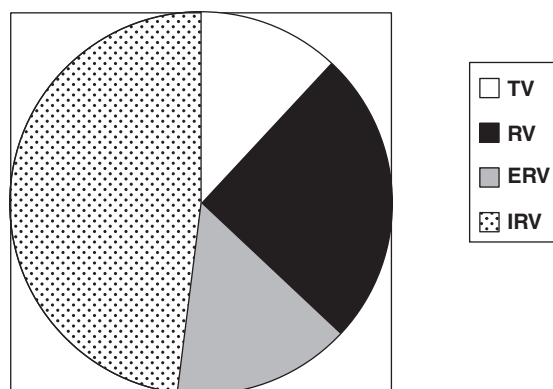


FIGURE 13–1 In the supine position, the gravid uterus compresses the inferior vena cava, decreasing venous return to the heart. This decrease results in a reduction in blood pressure and in cardiac output with an increase in heart rate. Usually, the term parturient may compensate with activation of the sympathetic nervous system. The parturient is unable to compensate if she is receiving anesthesia. In the supine position, cardiac output decreases typically 12% while blood pressure 20%. It is important to maintain left uterine displacement to avoid this supine hypotension syndrome. [Source: Based upon the data from Bamber JH. Aortocaval compression in pregnancy: the effect of changing the degree and direction of lateral tilt on maternal cardiac output. *Anesth Analg* 2003;97:256–258].

capacity of the lungs (FRC) at term. This decrease is a result of decreases in both residual and expiratory reserve volumes. Oxygen consumption increases by 20% due to increased metabolism and increased work of breathing. The parturient compensates for this increased oxygen consumption in two ways: (1) increased alveolar ventilation and (2) shifting the oxyhemoglobin dissociation curve to the right, thus facilitating unloading of oxygen at the cellular level (Fig. 13–2).

Nonpregnant



Pregnant

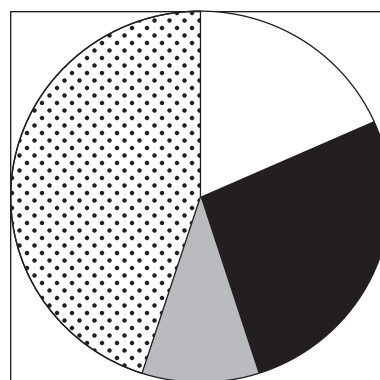


FIGURE 13–2 The gravid uterus presses against the diaphragm, decreasing the functional residual capacity. Total lung capacity is unchanged due to widening of the thoracic anteroposterior diameter. Tidal volume and respiratory rate increase with pregnancy. In going from nonpregnant to pregnant, the parturient experiences an increase in tidal volume, a decrease in expiratory reserve and residual volume, and no change in inspiratory reserve volume. [Source: Based upon the data from Skaredoff MN. Physiological changes during pregnancy: effects of major regional anesthesia. *Reg Anesth* 1981;1981:28].

3. The decrease in FRC and increased oxygen consumption make parturients very vulnerable to hypoxia. After complete denitrogenation by breathing 100% oxygen, nonpregnant patients tolerate 9 minutes of apnea before oxygen saturation is less than 90%, whereas parturients may only tolerate 2 to 3 minutes.
4. Alveolar ventilation increases by 70%. This increase results primarily from increased tidal volume and secondarily from a small increase in respiratory rate. The PaCO_2 decreases to 32 mm Hg as a result of increased ventilation and PaO_2 increases 5 to 10 mm Hg. Decreased serum bicarbonate from 26 mm Hg to 22 mm Hg through increased renal excretion results in a partially compensated respiratory alkalosis.

C Gastrointestinal changes

1. The third trimester and labor are the time periods in which the parturient is at the greatest risk for regurgitation and aspiration of gastric contents during induction of general anesthesia or any other loss of consciousness.

This is due to the following changes that occur in the third trimester. The enlarged gravid uterus displaces the stomach cephalad. This displacement changes the angle of the gastroesophageal junction, decreasing competence of the gastroesophageal sphincter. The uterus also displaces the pylorus upward and posteriorly.

D Hematologic changes

1. Plasma volume increases 45% but the red cell mass increases only 20%, leading to the physiologic (dilutional) anemia of pregnancy.
2. The increase in blood volume allows the parturient to tolerate the blood loss accompanying normal childbirth without hemodynamic consequences.

E Renal changes

1. Renal plasma flow and glomerular filtration rate (GFR) increase during the first trimester to 50% above normal by the fourth month. The increase in renal plasma flow and GFR results in an increased creatinine clearance, with a decreased blood urea nitrogen (BUN) and creatinine (Cr). BUN decreases 40% to 8 to 9 mg/dL, while creatinine decreases to 0.4 to 0.5 mg/dL.

F Central nervous system changes

1. The minimum alveolar concentration for inhaled anesthetics decreases up to 40% during pregnancy. The mechanism is unclear, although it may be related to progesterone (which has sedative activity) and endorphins. A concentration of an inhalation agent that may not produce loss of consciousness in nonpregnant patients may render pregnant women unconscious, placing the parturient at risk for aspiration.
2. Pregnant women require less local anesthetic to produce the same level of epidural or spinal block. In the epidural space, it may be partly due to epidural vein engorgement, thus decreasing the volume of the epidural space. However, this decreased requirement is seen in the first trimester, well before significant mechanical changes have occurred.

G Reproductive tract changes

1. The uterus weighs 50 to 70 g in the nonpregnant state and increases to 1.0 to 1.5 kg in pregnant women at term. Total uterine blood flow increases from 50 mL/min in nonpregnant women to 700 mL/min in pregnant women at term, representing approximately 10% of the cardiac output.

III

NEUROPATHWAYS OF OBSTETRIC PAIN

A First stage of labor

1. The pain resulting from the first stage of labor is primarily due to dilation of the cervix with consequent distention and stretching. Although cervical dilation accounts for the majority of the pain, there is also contribution from mechanoreceptors in the uterus.

2. The pain of the first stage of labor is a visceral pain. It occurs over the lower abdomen between the umbilicus and symphysis pubis, laterally over the iliac crest in a band-like distribution, and posteriorly in the skin and soft tissue over the lower lumbar spines (the dermatomal distribution of T10 to L1).
3. The location of this pain is explained by the innervation of the uterus and cervix and also by the concept of referred pain. The sensory nerves, which transmit noxious impulses from the uterus and cervix, enter the spinal cord at T10, T11, T12, and L1. These fibers synapse in the spinal cord in the same location as the cutaneous fibers from these spinal cord levels. The brain interprets the increased firing in the spinal cord as originating from the cutaneous fibers and refers the pain to the abdomen, back, and hips.

B Second stage of labor

1. Second stage pain occurs as the fetus descends through the birth canal. This results in stretching and tearing of fascia, skin, and subcutaneous tissue.
2. The pain of the second stage of labor is a somatic pain. It is transmitted through the pudendal nerve, which is derived from the anterior primary divisions of the sacral nerves, S2, S3, and S4.
3. Unlike the diffuse discomfort of the first stage of labor, the pain of the second stage is localized to the perineum.

IV

ANALGESIA FOR LABOR

A Epidural analgesia

1. Epidural blockade plays a prominent role in obstetrics and obstetric anesthesia. To successfully use epidural blockade, the anesthesiologist must be able to locate the epidural space.
2. The epidural space is immediately peripheral to the dura mater. It extends from the foramen magnum to the sacral hiatus. The posterior longitudinal ligament forms the anterior boundary of this space, while the ligamentum flavum forms the posterior boundary. The pedicles and intervertebral foramina form the lateral boundaries.
3. The contents of the epidural space include the nerve roots, fat, lymphatic tissue, and blood vessels.
4. To locate the epidural space, a needle with attached syringe containing air or saline is advanced relying on the anesthesiologist's sense of feel through the ligament. The epidural space is identified when there is "loss of resistance" with injecting the saline or air. It is not possible to inject air or saline into ligament but it is possible to inject it when the needle enters the epidural space. Once the epidural space is located with the needle, a catheter is passed and various combinations of local anesthetic and opioid are administered (Fig. 13-3).

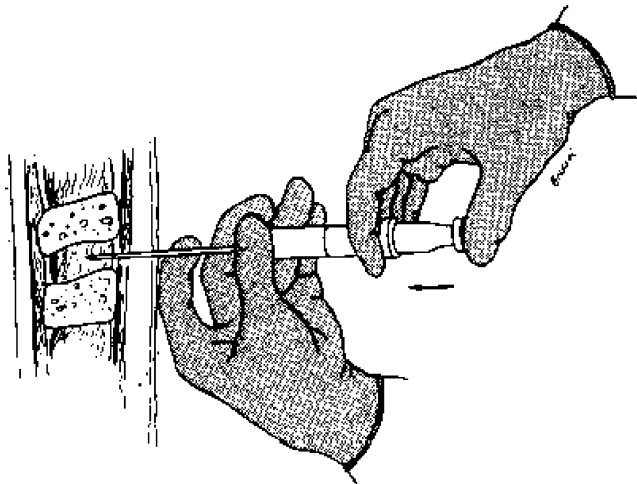


FIGURE 13-3 The technique of identifying the epidural space involves a loss of resistance. When the needle is engaged in ligament, it is not possible to inject air or saline. When the needle is advanced beyond the ligamentum flavum, it is possible to inject air or saline. [Source: Figure 13-3: Figure 8.10, page 126, Shnider and Levinson's Anesthesia for Obstetrics, fourth edition, 2002, LWW].

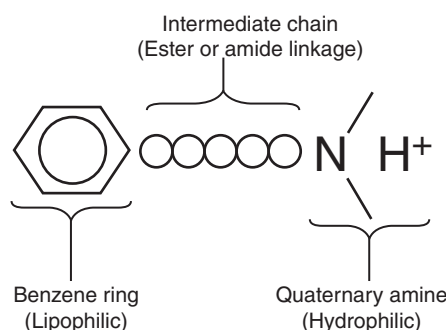


FIGURE 13–4 The general structure of a local anesthetic includes a lipophilic benzene ring and a hydrophilic carbon chain bearing a quaternary amine. The intermediate chain determines the class of local anesthetic. [Source: Figure 13–4: Figure 17–7, page 457, *Clinical Anesthesia*, fifth edition, 2006, LWW].

5. Epidural medications

a. Local anesthetics

- (1) Local anesthetics are a group of drugs that reversibly block nerve conduction.
- (2) All local anesthetics are weak bases that have a three-part structure: a lipophilic aromatic ring, an intermediate chain, and a hydrophilic carbon chain bearing an amino group. The intermediate chain determines to which classification a local anesthetic belongs. The esters have the COO configuration, while amides have the NHCO configuration (Fig. 13–4).
- (3) Local anesthetics prevent impulse generation in the nerve by gaining access to the sodium channel and blocking permeability to sodium ions.
- (4) Local anesthetics have their major toxic effects in the brain and myocardium. The brain is more susceptible than the heart to the toxic effects. With local anesthetic toxicity, seizures present before myocardial dysfunction. The main treatment for local anesthetic toxicity is intravascular intralipid. All anesthetizing locations where local anesthetics are used must have intralipid readily available.
- (5) Parturients are more sensitive to the neural blocking properties of local anesthetics. Pregnancy does not increase the risk of cardiac toxicity as compared to a nonpregnant individual. Table 13–2 lists the commonly used local anesthetics in obstetrics while Table 13–3 lists the manufacturer’s recommended upper limits.
- (6) The major goal of epidural analgesia is to maintain the patient’s motor function. As such, a dilute concentration of local anesthetic is used for analgesia.

b. Opioids

- (1) Opioids are frequently added to the local anesthetic solution in the epidural space. The opioids provide analgesia and allow for a lower dose of local anesthetic to be used. By using a low dose of opioid and local anesthetic, side effects of both are reduced.

TABLE 13–2 Individual Local Anesthetics

Ester Agents

Chloroprocaine	rapid onset, short duration
Tetracaine	long duration

Amide Agents

Lidocaine	first amide; intermediate duration; the most versatile, used topical, infiltrate, and intravenously, inhibits ventricular arrhythmias
Bupivacaine	long duration; prone to CV toxicity
Ropivacaine	S(–) optical isomer; long duration; chemically related to mepivacaine and bupivacaine, less cardiotoxic than bupivacaine
Levobupivacaine	the S(–) optical isomer of bupivacaine; analgesic profile identical to bupivacaine; less cardiotoxic than bupivacaine

TABLE 13–3 Manufacturer's Recommended Maximum Dose

Drug	Without Epinephrine (mg/kg)	With Epinephrine (mg/kg)
Lidocaine	5	7
Bupivacaine	3	3

- (2) By using a low concentration of opioid, the exposure of the neonate to the opioid is minimal.
- (3) The most common opioids added to the local anesthetic are the lipid-soluble ones, fentanyl and sufentanil. With high lipid solubility, cephalic spread is limited.
6. Risks of epidural analgesia are hypotension from sympathetic blockade and postdural puncture headache if the epidural needle should accidentally puncture the dura. Epidural analgesia does not increase the risk of cesarean delivery. It may increase the risk of operative vaginal delivery if the patient experiences motor blockade. There are some studies suggesting that it may interfere with the infant's ability to breastfeed, although this risk is associated with higher amounts of epidural fentanyl. Epidural analgesia may also prolong the duration of labor, usually 30 to 60 minutes.
 - a. The hypotension results from sympathetic blockade with venous dilation in the lower extremities.
 - b. The hypotension is treated with an intravenous fluid bolus of an isotonic solution that does not contain glucose. A vasopressor such as phenylephrine or ephedrine is also used.
 - c. The incidence of postdural puncture headache is 1% to 2% of all epidural analgesics performed. Postdural puncture headache results if the dura is punctured with the epidural needle. It is a postural headache that is located in the frontal–occipital area that is treated by an epidural blood patch. An epidural blood patch involves the injection of autologous blood into the epidural space.
7. Pain at the needle insertion site is probably the most common complication. It is usually secondary to a small bruise at the site and lasts for approximately 3 days. No study has been able to link epidural analgesia to backache.

B Combined spinal epidural analgesia

1. The epidural needle is placed into the epidural space. Before threading the epidural catheter, a long spinal needle is advanced through the epidural needle into the subarachnoid space. Following the injection of medication through the spinal needle, it is removed and the epidural catheter is placed.
2. The spinal injection typically consists of a small amount of local anesthetic combined with fentanyl. The most common local anesthetic is bupivacaine (0.25%) 1 mL (2.5 mg) and the most common opioids are fentanyl 25 µg or sufentanil 10 µg. The duration of analgesia from the opioid depends upon the stage of labor and patient genomics. The change of one amino acid in a DNA sequence may alter the response to the intrathecal opioid.
3. The intrathecal injection provides analgesia of rapid onset. The major difference between the combined spinal epidural and traditional epidural analgesia is the speed of onset of analgesia (1 to 2 minutes vs. 15 to 20 minutes). After 20 minutes, there is no difference in analgesia or maternal satisfaction between the two techniques.
4. The most common side effect of intrathecal fentanyl and sufentanil is pruritus.
5. Strict aseptic technique must be observed as combined spinal epidural analgesia involves dural puncture and the subsequent risk of meningitis.

C Intravenous analgesia

1. Patients with clotting disorders, thrombocytopenia, or previous spinal surgery may not be candidates for epidural analgesia. Intravenous patient-controlled analgesia (PCA) should be considered for these patients.

- a. Fentanyl
 - (1) Fentanyl is probably the best opioid for PCA. It has less sedation and nausea associated with it. It is also associated with a lower placental transfer.
 - (2) The loading dose is 1 to 2 $\mu\text{g}/\text{kg}$. Patients do not receive a continuous infusion, rather a bolus of 50 μg with a lockout of 10 minutes.
- b. Morphine
 - (1) Morphine is used early in labor but not as PCA. It is administered in a dose of 10 mg IM or 2 to 5 mg IV, usually during a prolonged latent phase.
- c. Nalbuphine
 - (1) Nalbuphine is also not used in PCA and is administered as a bolus. It is a synthetic agonist-antagonist (in low doses it acts at the μ receptor as an agonist; in higher doses, its antagonist properties prevail preventing respiratory depression).
 - (2) The usual dose is 10 mg IV or IM.
2. Naloxone is capable of reversing the effects of opioids such as respiratory depression or pruritus. It also reverses the analgesia of opioids.
3. Intravenous opioids decrease fetal heart rate variability. Even with the low placental transfer, there is approximately a 20% incidence of the need for naloxone in the neonate.

D Other regional blocks

1. Paracervical block
 - a. The fibers innervating the uterus and cervix leave the cervix and join the sensory nerves that accompany the sympathetic nerves of T10 to L1.
 - b. Paracervical block involves the injection of local anesthetics submucosally into the fornix of the vagina laterally to the cervix (generally at 4 o'clock and 8 o'clock). The somatic sensory fibers of the perineum are not blocked.
 - c. Paracervical block is effective only for the first stage of labor, and is associated with a high incidence of fetal bradycardia.
 - d. Its major role is in providing analgesia for dilation and curettage.
2. Pudendal block
 - a. Somatic pain of the second stage of labor results from distention of the pelvic floor, vagina, and perineum as the fetus descends through the birth canal. These painful impulses are transmitted primarily through the pudendal nerve, which is derived from the anterior primary divisions of the sacral nerves S2 to S4.
 - b. Pudendal block involves the injection of local anesthetic below the ischial spines (the approximate location of the pudendal nerve). This block is administered during the second stage of labor and is useful for vaginal delivery and outlet forceps. It is also helpful for suturing following delivery as it anesthetizes the perineum.

V

ANESTHESIA FOR CESAREAN DELIVERY

- A** Anesthesia for cesarean delivery may be divided into two different types: general and regional. The decision regarding the type depends upon the urgency of the cesarean delivery, comorbidities, and patient's desires.

B Spinal anesthesia

1. Spinal anesthesia for cesarean delivery involves the subarachnoid injection of sufficient local anesthetic to achieve a T4 sensory level (mid-chest level) to insure patient comfort during the procedure.
2. Spinal anesthesia involves a single needle that is advanced into the subarachnoid space. It is chosen when the length of the procedure is known as it does not permit reinjection. The duration of the spinal anesthetic depends upon the local anesthetic chosen and upon the addition of epinephrine to the injectate. If the duration of the procedure is in question, a continuous technique is preferred.
3. The major risks of spinal anesthesia include postdural puncture headache, maternal bradycardia, maternal hypotension, and limited duration of action (if the procedure lasts longer than the

spinal anesthetic, general anesthesia is administered). The risk of headache may be reduced by using a spinal needle with a pencil point tip as compared to a cutting tip that is typically used for lumbar puncture.

4. It takes approximately 5 to 7 minutes to perform a spinal anesthetic and to achieve an appropriate sensory level of anesthesia for cesarean delivery.
5. Hypotension from spinal anesthesia is treated with phenylephrine 100 µg or ephedrine 10 mg. Currently, if the mother is not bradycardic, phenylephrine is preferred due to its favorable umbilical cord pH.
6. Spinal anesthesia results in denser sensory blockade and may result in maternal bradycardia from blockade of the cardiac accelerator fibers (T1 to T4). There are case reports of maternal asystole from spinal anesthesia.

C Epidural anesthesia

1. Surgical anesthesia may be achieved in 2 to 3 minutes in a patient with an epidural catheter placed for labor.
 - a. The use of 1.5% lidocaine with epinephrine 1:200,000 achieves a T4 sensory level within 4 to 6 minutes.
 - b. The use of 3% 2-chloroprocaine with sodium bicarbonate achieves a T4 sensory level within 2 to 3 minutes.
 - c. The choice of drug depends upon the urgency of the situation.
2. The presence of an epidural catheter allows the administration of additional local anesthetic if the procedure should be prolonged. It takes approximately 8 to 12 minutes to place an epidural catheter.
3. Approximately 20 mL of local anesthetic is required to achieve a T4 sensory level. The higher volume places the patient at risk for local anesthetic toxicity if injected intravascularly and excessive sensory blockade if injected subarachnoid.
4. The incidence of maternal bradycardia is less with epidural anesthesia.
5. Neurologic injury is more related to the birth process rather than the epidural anesthetic. Both epidural and spinal anesthesia may result in neurologic injury. The presentation is typically a sensory deficit in a dermatomal distribution. This injury is accompanied by a paresthesia during needle placement or injection of local anesthetic. The presence of a paresthesia requires removal of the needle and replacement at another location to prevent injury.

D General anesthesia

1. General anesthesia for cesarean delivery is indicated in true emergency situations (general anesthesia takes approximately 1 to 2 minutes to have the patient ready for surgical incision), when the mother prefers, or when regional anesthesia is contraindicated (thrombocytopenia, coagulopathy, infection of the spine).
2. Clear antacids, metoclopramide, and histamine-2 blockers are suggested to reduce stomach contents and acidity to reduce the risk of the development of aspiration syndrome if the patient should aspirate.
3. To secure the airway, thiopental (or propofol) and succinyl choline are administered in rapid sequence with cricoid pressure (firm downward force on the cricoid cartilage to compress the esophagus). An endotracheal tube is placed. Failure to secure the endotracheal tube in a timely fashion may result in maternal hypoxia with subsequent brain injury and death. This failure is the most common reason for maternal mortality from anesthesia.
4. When general anesthesia is given, neonatal depression (as quantified by reduced APGAR scores) occurs more frequently than for regional anesthesia. This depression may be worsened by delays from induction to delivery. APGAR scores are lower at 1 minute and show little difference at 5 minutes.
5. Awareness during general anesthesia is more common for cesarean delivery than for other types of surgery. Lower levels of anesthetic are administered to prevent neonatal depression. The inhalation agents used for general anesthesia relax the myometrium. Maternal awareness is prevented by maintaining low end-tidal concentrations of volatile agents.

E Postoperative analgesia

1. When cesarean section is performed during regional anesthesia, preservative-free morphine is administered with the intrathecal injection for spinal anesthesia or with the local anesthetic for epidural anesthesia. The use of preservative-free morphine provides analgesia of 12 to 24 hours' duration.
2. Administering doses higher than 4 mg of morphine in the epidural anesthetic or higher than 0.2 mg of morphine in the spinal anesthetic does not improve the duration of analgesia. It does increase the incidence of side effects such as pruritus or respiratory depression.
3. Postoperative orders should include respiratory monitoring and treatment if it should occur.
4. If epidural anesthesia was used, patients occasionally receive continuous infusions of low concentration local anesthetic postoperatively for analgesia.
5. When cesarean delivery is performed during general anesthesia, PCA is typically used for postoperative analgesia. The opioid chosen is morphine, as it has the fewest effects on the neonate if the mother is breastfeeding.
6. Patients usually receiving ondansetron following cesarean delivery as prophylaxis for postoperative nausea vomiting.

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Study Questions for Chapter 13

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A 24-year-old parturient is at 24 weeks' gestation. Her past medical history is notable for mitral stenosis secondary to rheumatic heart disease as a child. What physiologic change of pregnancy places her at risk for the development of heart failure?

- ☐ A Decreased functional residual capacity
- ☐ B Increased red cell mass
- ☐ C Increased uterine blood flow
- ☐ D Decreased creatinine concentration
- ☐ E Increase in stroke volume

2. A parturient at 40 weeks' gestation is scheduled for a magnetic resonance imaging scan to assess for placenta accreta. The radiologist is unable to complete the study due to nausea whenever the patient is supine. What therapeutic would you recommend to the radiologist?

- ☐ A Antiemetic medication
- ☐ B Fasting prior to the study
- ☐ C Intravenous fluid
- ☐ D Tilting the patient to the left
- ☐ E Supplemental oxygen

3. A 24-year-old parturient with severe preeclampsia requires urgent cesarean delivery for nonreassuring fetal heart rate. The anesthesiologist plans general anesthesia. Which of the following physiologic changes of pregnancy increases the risk of the inability to place an endotracheal tube in this patient?

- ☐ A Increased tidal volume
- ☐ B Edema of the larynx
- ☐ C Nasal congestion
- ☐ D Delayed gastric emptying
- ☐ E Shift of oxygen saturation curve

4. Which of the following regional anesthetic techniques would NOT be effective for the first stage of labor?

- ☐ A Epidural
- ☐ B Combined spinal epidural
- ☐ C Paracervical
- ☐ D Pudendal
- ☐ E Lumbar sympathetic

5. A 25-year-old G1P0 parturient requests labor epidural analgesia. During epidural placement, the dura mater is punctured. Which of the following postdelivery complications are the risks increased in this patient?

- ☐ A Hypotension
- ☐ B Postdural puncture headache
- ☐ C Backache
- ☐ D Respiratory depression
- ☐ E Nerve injury

6. A 32-year-old G3P2002 parturient requires elective repeat cesarean section for previous vertical incision. The decision was to use epidural anesthesia. Following the injection of 20 cc 2% lidocaine, the patient seizes and develops ventricular tachycardia. Which of the following medications is the most appropriate therapeutic in this situation?

- ☐ A Magnesium
- ☐ B Amiodarone
- ☐ C Defibrillation
- ☐ D Intralipid
- ☐ E Epinephrine

7. A 21-year-old parturient is considering epidural analgesia. She would like to know which of the following is increased in patients with epidural analgesia?

- ☐ A Prolonged labor
- ☐ B Cesarean delivery
- ☐ C Neonatal depression
- ☐ D Cerebral palsy
- ☐ E Episiotomy

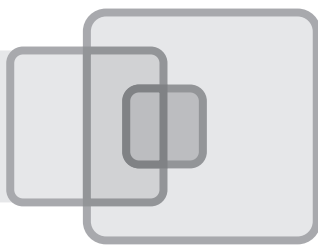
8. A 35-year-old parturient is at 4 cm cervical dilation and does not have an epidural catheter in place. The obstetrician decides to rupture the membranes. Following rupture of the membranes, the umbilical cord has prolapsed through the cervix into the vagina. The obstetrician needs to perform an urgent cesarean section in this patient. Which of the following is the most appropriate anesthetic technique for this patient?

- ☐ A Paracervical block
- ☐ B Pudendal block
- ☐ C Spinal block
- ☐ D Epidural block
- ☐ E General anesthesia



Answers and Explanations

1. **The answer is E** (II A a). During pregnancy, the cardiac output increases. This increase occurs as a result of an increase of both stroke volume and heart rate. A parturient with a fixed cardiac lesion such as mitral or aortic stenosis cannot increase her cardiac output to meet the increased demands placed upon her, and as such, is at risk for the development of heart failure. A decrease in functional residual capacity results in hypoxemia during periods of apnea. While the red cell mass and plasma volume are increased, the increase is generally well tolerated by an individual with cardiac disease.
2. **The answer is D** (II A e). Approximately 15% of patients develop symptoms of nausea when supine. In this position, the gravid uterus compresses the vena cava and decreases venous return. This in turn decreases cardiac preload and cardiac output. If these symptoms develop, it is important to tilt the patient to the left or place a wedge under her right hip. Not all patients develop these symptoms because of sympathetic compensation. Patients with anesthesia must be maintained in the left uterine displacement position as they do not possess the ability for sympathetic compensation.
3. **The answer is B** (II B a). Airway edema occurs during pregnancy and may be worsened by preeclampsia. It is important to have small-diameter endotracheal tubes available prior to starting anesthesia in a patient with preeclampsia. Delayed gastric emptying increases the risk of aspiration. The shift of the oxygen saturation curve decreases the time available for intubation. Increased tidal volume and nasal congestion have no effect on the ability to place an endotracheal tube.
4. **The answer is D** (III B b). Pain for the first stage of labor results primarily from the cervix and uterus. The fibers innervating the uterus and cervix leave the cervix (paracervical block) and join the sympathetic fibers (lumbar sympathetic) of T10, T11, T12, and L1. These fibers then synapse in the spinal cord (epidural and combined spinal epidural) at these levels in the same area that the fibers from the skin of these dermatomes. The brain refers the pain from the cervix to these areas of the skin, accounting for the pain of the first stage of labor. Second stage pain is transmitted by the pudendal nerve.
5. **The answer is B** (IV A f iii). Postdural puncture headache is a bilateral headache that develops within 7 days after dural puncture and usually disappears 14 days after the dural puncture. It worsens within 15 minutes of assuming the upright position and improves within 30 minutes of resuming a recumbent position. It usually occurs in the frontal, occipital, or both areas. Postdural puncture headache occurs because of the leakage of cerebrospinal fluid into the epidural space from a hole in the dura. This leakage results in intracranial hypotension and causes the headache. Backache and hypotension occur with epidural analgesia but the risk is not increased with a dural puncture. Nerve injury results from trauma to the needle and accompanies paresthesias, not dural punctures.
6. **The answer is D** (IV A e i 4). If accidentally administered intravascularly, local anesthetics may cause central nervous system and cardiac toxicity. Local anesthetics are lipid soluble and increasing the lipid concentration in the blood draws local anesthetic from the brain and heart into the blood stream. Intralipid should be available in any anesthetizing location in which local anesthetics are used.
7. **The answer is A** (IV A f). Epidural analgesia does not increase the risk of cesarean section. The fetus is exposed to minimal medication. It does not result in a depressed neonate. Multiple studies indicate that labor is prolonged in patients with epidural analgesia.
8. **The answer is E** (V D i). Paracervical block and pudendal block provide analgesia for labor and are insufficient for cesarean delivery. Umbilical cord prolapse may affect umbilical blood flow and is considered a true obstetric emergency, requiring expeditious delivery. Both spinal and epidural anesthesia would need too much time to establish satisfactory anesthesia. General anesthesia, although associated with greater risk, may be established in 1 to 2 minutes.



Postterm Pregnancy

ABIKE JAMES

I

INTRODUCTION

Postterm pregnancy is a pregnancy that has extended beyond 42 weeks of gestation. The prevalence of postterm pregnancy varies but is estimated to occur in 5% to 10% of all pregnancies. Postterm pregnancy is associated with increased risk of fetal, maternal, and neonatal complications. As such, awareness of this condition is important and management remains a matter of concern for clinicians.

II

DEFINITION

Term gestation is defined as a pregnancy between 37 and 42 completed weeks (260 to 294 days) after the first day of the **last menstrual period (LMP)**. Postterm pregnancy begins when 42 completed (menstrual) weeks have elapsed. The first day of the LMP occurs approximately 2 weeks before conception in a 28-day cycle.

III

DETERMINING GESTATIONAL AGE

An accurate assessment of gestational age is essential to identifying postterm pregnancy.

Listed below are several methods used to determine gestational age:

- A** **Naegele's rule** uses the first day of the LMP to calculate the **estimated date of confinement (EDC)**. Assuming a 28-day cycle, subtract 3 months and add 7 days to the first day of the LMP to determine the delivery date. It is important to remember that if a woman's menstrual cycle is 35 days rather than 28 days, then she would ovulate on CD 21 rather than CD 14 and this would shift the EDC by 1 week.
- B** **Quickening** is the maternal perception of fetal movement and begins around 16 to 20 weeks of gestation.
- C** Uterine size increases with gestational age. The uterus is a pelvic organ until 12 weeks, at which time the **fundus** can be palpated at the level of the iliac crests. The uterine fundus is palpable at the umbilicus around 20 weeks. Between 20 and 36 weeks, the measurement of the uterus in centimeters from the symphysis pubis to the fundus approximates the gestational age within 2 weeks.
- D** An electronic Doppler ultrasound may detect fetal heart tones as early as 10 to 11 weeks' gestation.
- E** Ultrasound examination in the first trimester provides the most accurate determination of gestational age. Measurement of the **crown-rump length (CRL)** is accurate to within 5 to 7 days of the actual gestational age. The second- and third-trimester ultrasound uses several parameters for determining gestational age. These parameters include the **biparietal diameter (BPD)**, the **femur length (FL)**, and the **abdominal circumference (AC)**. In the second trimester, the BPD is the most accurate but only to within 14 days of the actual gestational age. Measurements in the third trimester may have an error up to ± 21 days of the actual gestational age. If the estimated gestational age by LMP differs from the ultrasound estimate by more than the acceptable number of day's variation, then the ultrasound estimation of gestational age should be used instead of the LMP-based estimate. The use of ultrasound in determining the EDC has been shown to decrease the incidence of postterm pregnancy from 12% to 3%.

IV

ETIOLOGY OF POSTTERM PREGNANCY

The most frequent cause of an apparent postterm pregnancy is error in determining the time of ovulation and conception based on the reported LMP. Frequently encountered problems are the patient's failure to recall the date of her LMP and the variable length of the proliferative phase of the cycle, which allows for variation in the ovulation date. **When postterm pregnancy truly exists, the cause is usually unknown.** Common risk factors for postterm pregnancy include nulliparity and previous postterm pregnancy. Male fetuses and obesity have also been shown to be associated with increases in prolongation of pregnancy. Parturition (the process of giving birth) is a complex process that involves events within the fetal brain, adrenals, placenta, amnion, and chorion; it induces changes in the maternal tissues, including the decidua, myometrium, and cervix. The theorized mechanism of parturition begins with a stimulus in the fetal brain, resulting in **activation of the fetal hypothalamic–pituitary axis. Adrenocorticotrophic hormone** production results in stimulation of the **fetal adrenal**. The fetal adrenal increases production of **dehydroepiandrosterone sulfate (DHEAS) and cortisol**. The presence of **placental sulfatase** in the placenta is required so that the placenta can convert the DHEAS to **estradiol**. Estrogen is thought to be important in increasing myometrial activity, and cortisol is thought to be important in stimulating **prostaglandin** output in the placental tissues. Prostaglandins are important for myometrial contractility. Several disorders may result in delayed parturition and postterm pregnancy. These disorders are all similar in that they are associated with low estrogen production. **These rare causes of postterm pregnancy include:**

- A Anencephaly** is an absence of the fetal cranium with gross abnormalities associated with the fetal brain. The absence and abnormalities of these structures prevent the normal initiation of parturition and result in prolonged gestation.
- B Congenital primary fetal adrenal hypoplasia** has been associated with prolonged gestation. The fetal adrenal is important in the production of cortisol and androgens, which help parturition to occur.
- C Placental sulfatase** is required to convert fetal DHEAS to estrogen. Deficiency of placental sulfatase leads to decreased estrogen levels and a subsequent delay in parturition. This is an X-linked disorder that affects male fetuses, occurring in 1 in 2,500 newborns.

V

COMPLICATIONS OF POSTTERM PREGNANCY

Postterm pregnancies are associated with an increase in fetal, maternal, and neonatal adverse events. These include **an increase in stillbirth rates, a higher incidence of meconium and meconium aspiration syndrome, prolonged labor, operative vaginal delivery, shoulder dystocia, macrosomia, oligohydramnios, fetal heart rate abnormalities, and cesarean section.**

VI

MANAGEMENT OF THE POSTTERM PREGNANCY

The goal of management of postterm pregnancy is to decrease the risk of an adverse perinatal outcome (including stillbirth). Two management strategies are commonly utilized. The first is the prevention of postterm pregnancy by inducing labor and the second is expectant management under close surveillance. Older studies have suggested that routine induction of labor prior to 41 weeks increases the risk of cesarean delivery, particularly in nulliparous women. The findings from randomized trials in the 1990s are equivocal on the advantages or disadvantages of routine induction versus expectant management. Therefore, both management strategies are acceptable.

- A Induction of Labor** The success of labor induction is dependent on the characteristics of the cervix. A cervix is determined to be favorable by its Bishop score (Table 14–1). Induction is usually successful with a score of 9 or greater. A Bishop score of less than or equal to 4 is considered to be unfavorable for induction.
- B Expectant management under close surveillance** When expectant management is undertaken, close surveillance is necessary. This surveillance is termed **antenatal testing. Antenatal**

TABLE 14–1 Bishop Scoring System Used for Assessment of Inducibility

Score	Cervical				
	Dilation	Effacement (%)	Station	Consistency	Position
1	Closed	0–30	–3	Firm	Posterior
2	1–2	40–50	–2	Medium	Midposition
3	3–4	60–70	–1.0	Soft	Anterior
4	>5	>80	+1, +2	—	—

Reprinted with permission from Cunningham FG, MacDonald PC, Gant NF. Williams Obstetrics. 21st Ed. New York: McGraw-Hill, 2001:471, Table 20–1.

testing is generally **occurs twice weekly between 41 and 42 weeks' gestation**. It can include the **nonstress test (NST)**, the **contraction stress test (CST)**, or the **biophysical profile (BPP)** (see Chapters 6 and 11).

1. The **NST** is a noninvasive test of fetal activity that correlates with fetal well-being. Fetal heart rate (FHR) accelerations are observed during fetal movement. An external monitor is used to record the FHR, and the mother participates by indicating fetal movements.
 - a. A **reactive test** requires **two FHR accelerations** of at least 15 beats' amplitude of 15 seconds' duration in a 20-minute period.
 - b. In one study, 99% of oxytocin challenge tests were negative for signs of fetal distress when performed after a reactive NST.
 - c. The most common cause for a nonreactive NST is a period of fetal inactivity or sleep. Studies have shown that the longest interval of fetal inactivity in the healthy fetus is 40 minutes.
 - d. If the test is nonreactive after 40 minutes, a BPP or CST is indicated.
 - e. Approximately 25% of fetuses that have a nonreactive NST have a positive CST.
2. The **CST** is a test of FHR that indirectly measures placental function in response to uterine contractions. An intravenous infusion of oxytocin is used to stimulate uterine contractions. The nipple stimulation test is an endogenous means of releasing oxytocin in response to manual stimulation of the patient's nipples. It can be viewed as a noninvasive CST.

A CST result may be classified as **negative, positive, or equivocal**.

 - a. A **negative CST** consists of three uterine contractions of moderate intensity lasting 40 to 60 seconds over a 10-minute period with no late decelerations in the FHR tracing. A **positive CST** has late decelerations associated with more than 50% of the uterine contractions. A CST with inconsistent late decelerations is considered equivocal.
 - b. More often, a favorable outcome follows a negative CST, but as many as 25% of fetuses may experience intrapartum fetal distress after a negative CST.
 - c. CSTs have a **25% false-positive rate**.
 - d. Studies have shown the incidence of perinatal death within 1 week of a negative CST to be less than 1 in 1,000. Most of these deaths are caused by cord accidents or abruptions.
 - e. A positive CST has been associated with an increased incidence of intrauterine death, late decelerations in labor, low 5-minute APGAR scores, intrauterine growth retardation, and meconium-stained amniotic fluid. The overall perinatal death rate after a positive CST is between 7% and 15%.
 - f. If a patient over 41 weeks' gestation undergoing a CST has an equivocal or positive result, delivery should be strongly considered.
3. **Biophysical profile** (see Chapter 6) is a composite of tests utilizing FHR tracing and ultrasound designed to identify a compromised fetus during the antepartum period (Table 14–2).
 - a. **Components of the profile**
 - (1) NST
 - (2) Fetal breathing
 - (3) Fetal tone
 - (4) Fetal motion
 - (5) Quantity of amniotic fluid

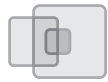
TABLE 14-2 Management Based on BPP Score

Score	Interpretation	Management
10	Normal	Repeat testing
8	Normal	Repeat testing
6	Suspect chronic asphyxia	If >36 weeks, deliver Repeat testing in 4–6 hours
4	Suspect chronic asphyxia	If >32 weeks, deliver Repeat testing in 4–6 hours
0–2	Strongly suspect chronic asphyxia	Extend testing to 120 minutes; if score ≤ 4 , deliver at any gestational age

b. Scoring of the profile. Each test is given either 2 or 0 points, for a maximum of ten points. An important feature in the postterm profile is the **amniotic fluid index (AFI)**. **Oligohydramnios (AFI less than 5)** is an ominous sign that signifies placental insufficiency and increased risk of poor perinatal outcome. Term patients with oligohydramnios should be delivered.

C Timing of delivery **Delivery is indicated** when the risks to the fetus, mother, or both associated with continuation of the pregnancy are greater than those faced during or after delivery. As such, pregnant women with conditions such as diabetes or hypertension are at high risk of maternal and fetal complications and are generally delivered by 40 weeks' gestation. In low-risk women, induction of labor may be performed at 41 weeks if the cervix is favorable. If the cervix is unfavorable, then expectant management with antepartum fetal surveillance should be continued. Any abnormal antenatal testing should lead to an intervention that either provides reassurance or proceeds toward delivery. Generally, at 42 weeks' gestation, if the cervix remains unfavorable, prostaglandins are administered to "ripen" the cervix for induction.

D Intrapartum management includes continuous electronic FHR monitoring.



Study Questions for Chapter 14

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A 33-year-old woman, gravida 2, para 1, who is in the third trimester presents to you for her first prenatal care. She is not sure of her due date because she has been given three different dates by three different doctors. She tells you that her periods are irregular and occur every 21 to 35 days. She has not taken any form of birth control for the past 2 years. The first day of her LMP was July 19, 2010. You obtain a record of an ultrasound performed in the emergency room on September 5, 2010, which showed her to be at 8 and 0/7 weeks of gestation. You also obtain a record from her last doctor who performed an ultrasound on December 22, 2010, which showed her to be at 24 and 3/7 weeks of gestation. Which one of the following is the best estimate of her due date? (You can use a pregnancy wheel.)

- ☐ A April 7, 2011
- ☐ B April 8, 2011
- ☐ C April 19, 2011
- ☐ D April 24, 2011
- ☐ E April 26, 2011

2. A 22-year-old woman, gravida 1, para 0, at 15 weeks of gestation by her LMP, presents to you for an ultrasound examination to confirm her due date. Which of the following measurements on the fetus is the best at predicting her actual due date?

- ☐ A Crown–rump length
- ☐ B Biparietal diameter
- ☐ C Abdominal circumference
- ☐ D Femur length
- ☐ E Head circumference

3. A 25-year-old woman, gravida 3, para 0, at 42 weeks of gestation, presents to your clinic for prenatal care. She has accurate dating and has been receiving twice-weekly NSTs for the last week. Underdevelopment of which structure in the fetus may contribute to prolongation of this woman's gestation?

- ☐ A Cerebral cortex
- ☐ B Thalamus
- ☐ C Thymus
- ☐ D Adrenal cortex
- ☐ E Ovary

4. A 22-year-old woman, gravid 1, presents at 41 and 1/7 weeks and her cervix is closed/long and high. You decide to expectantly manage her. Which of the following are your options?

- ☐ A NST twice weekly
- ☐ B Tell her to return in 1 week to be checked
- ☐ C BPP
- ☐ D All of the above
- ☐ E a and c

5. You perform a BPP on the patient in Question 4 and the AFI is 3. What is your next step?

- ☐ A Repeat the BPP in 6 hours
- ☐ B Repeat the BPP in 24 hours
- ☐ C Proceed with induction of labor
- ☐ D Perform an NST

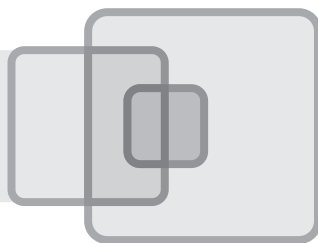
6. A 34-year-old woman, gravida 3, para 1, abortions 1, at 42 and 1/7 weeks of gestation by a Week-6 ultrasound, presents to your clinic. Her NST is reactive and AFI is 8.5. Her cervix is 0.5 cm dilated, 20% effaced, midposition, and firm, and the fetal vertex is at -4 station. Which of the following is the best next step in management?

- ☐ A Oxytocin
- ☐ B Cervical ripening with a prostaglandin analog
- ☐ C Twice-weekly NST
- ☐ D Repeat modified BPP (NST and AFV)
- ☐ E Artificial rupture of membranes (AROM)



Answers and Explanations

1. **The answer is C.** Because this patient has irregular periods, estimation of her due date by her LMP is inaccurate. Therefore, Naegele's rule cannot be used to determine her EDC because it assumes a regular 28-day cycle (April 26 is incorrect). Thus, the best estimate of her actual due date is provided by the first-trimester ultrasound. Using the pregnancy wheel, if you match September 5 with 8 weeks, then you will see that 40 weeks (due date) corresponds to April 16, 2008, ± 1 day (given inherent error between different pregnancy wheels). Because this is a first-trimester ultrasound, there can be a maximum of ± 7 days error. Therefore, the due date must fall between April 8 and April 24 (April 16 ± 8 days). April 19 is the best estimate of the actual due date.
2. **The answer is B.** In the second trimester (over 13 weeks), BPD is the most accurate at determining actual gestational age. CRL length is the most accurate in the first trimester. None of the other measurements is as useful at estimating gestational age except for the head circumference.
3. **The answer is D.** Fetal adrenal hypoplasia has been associated with prolongation of gestation. Anencephaly, not lack of cerebral cortex or thalamus, has been associated with prolongation of gestation. Anencephaly results in lack of the hypothalamic–pituitary axis, which is theorized to be responsible for the inception of parturition. The ovary is probably not involved in the initiation of labor. However, estrogen produced by placental conversion of DHEAS is thought to increase myometrial activity.
4. **The answer is E.** When the decision is made to expectantly manage, you need to begin antenatal testing. This can include an NST, BPP, or CST. It is not an option to just repeat an examination in 1 week.
5. **The answer is C.** An AFI of 3 is indicative of oligohydramnios. Any term patient with oligohydramnios should be delivered. There would be no benefit to repeating the BPP.
6. **The answer is B.** At 42 weeks of gestation, if the cervix remains unfavorable, as in this case (her Bishop score is $1 + 1 + 1 + 1 + 2 = 6$), prostaglandins will be administered to “ripen” the cervix for induction. Use of oxytocin for induction of an unfavorable cervix results in prolonged labor and increases the possibility of cesarean section. AROM is not a good idea if the fetal vertex is very high (-4 station). You should never send a postterm patient (more than 42 weeks) home to follow up with twice-weekly NSTs because the perinatal mortality rate is very high. There is no reason to repeat the modified BPP because this one is reassuring.



Preterm Labor

VANITA DHARAN JAIN • MICHAL A. ELOVITZ

I

PRETERM BIRTH

A Definition Preterm infants are born **before 37 weeks' gestation** (less than 259 days from the date of the last menstrual period). Preterm birth is a major contributor to neonatal morbidity and mortality. Furthermore, ex-preterm children are at significant risk for developmental delay, visual and hearing impairment, chronic lung disease, and cerebral palsy. In the United States, preterm birth is the leading cause of neonatal mortality (less than 28 days of life) and of African American infant mortality (less than 365 days of life). Neonates born before 32 weeks have the greatest risk for poor health outcome and death. Those born between 32 and 36 weeks are still at higher risk for health and developmental problems than those born full term.

B Epidemiology In 2006, preterm birth accounted for 12.8% of all live births in the United States—an increase of 20% since 1990. According to estimates by the World Health Organization among the 130 million infants born each year worldwide, 8 million die due to prematurity. Much of the increase is a result of an increase in the number of multiple gestations secondary to fertility treatment. Preterm births account for more than 60% of non-anomaly-related neonatal mortality and morbidity.

1. **“Spontaneous” preterm birth.** Seventy-five percent of preterm births occur spontaneously after preterm labor and preterm premature rupture of membranes (PPROM).
2. **“Indicated” preterm birth.** Twenty to thirty percent of all preterm births occur because of a medical or obstetric disorder that places the mother or fetus at significant risk for serious morbidity or mortality.
3. Neonatal morbidity and mortality increase as the gestational age at delivery decreases.

II

RISK FACTORS FOR PREMATURE DELIVERY

In the United States, 17% to 34% of infant deaths are attributable to prematurity, but only about half of the cases of prematurity result from an identifiable cause.

A Sociodemographic factors

1. **Low socioeconomic status.** Low income, low level of education, and poor nutrition are associated with preterm delivery.
2. **Ethnicity.** In the United States, the rate of preterm birth among black women is twice as high and the rate of recurrent preterm birth four times as high, as the rate among white women.
3. **Age.** Maternal age of 18 years or less or of 40 years or more increases the risk of preterm delivery.
4. **Previous premature birth.** The risk in the subsequent pregnancy after prior premature birth is 15% to 56%, depending on the presence of other risk factors.

B Maternal medical and obstetric conditions

1. **Uterine conditions**
 - a. **Müllerian malformations.** Women with unicornuate, bicornuate, didelphic, or septate uteri are at increased risk of preterm delivery.

- b. **Cervical insufficiency.** Traditionally, cervical insufficiency is defined as painless cervical dilation in the second trimester and is associated with eventual pregnancy loss. It can be caused by trauma during an obstetric or gynecologic procedure, cervical cone biopsy, diethylstilbestrol exposure in utero, or unknown etiology. However, distinguishing patients with cervical insufficiency from early preterm delivery remains difficult.
- c. **Uterine overdistention**
 - (1) Polyhydramnios (amniotic fluid index of more than 25 cm).
 - (2) Multiple gestations. Twin intrauterine pregnancies have a preterm labor rate of approximately 40%. Triplet intrauterine pregnancies have a 25% risk of delivery prior to 24 weeks' gestation and a 10% delivery rate from 24 to 28 weeks' gestation. The average gestational age at delivery for twins is 36 to 38 weeks and for triplets 32 to 34 weeks.
- 2. **Obstetric conditions.** These conditions result in medically indicated preterm births
 - a. Preeclampsia–eclampsia
 - b. Placenta abruption
 - c. Placenta previa
 - d. Fetal growth restriction
 - e. Prematurely ruptured membranes
- 3. **Other maternal conditions.** These disorders include chronic hypertension, diabetes mellitus type 1, renal disease, osteogenesis imperfecta, and collagen vascular disease.

C Infection Significant maternal infections that may cause preterm labor and delivery include:

- 1. Systemic infections
 - a. Pyelonephritis
 - b. Pneumonia
- 2. Local infections
 - a. Bacterial vaginosis (This is associated with preterm rupture of membranes, but it remains unclear if there is a mechanistic association.)
 - b. Subclinical and clinical intra-amniotic infections
 - c. Sexually transmitted diseases (STDs) (very poorly defined relationship with preterm labor)

III

PREVENTION OF PRETERM BIRTH

A Secondary prevention

- 1. **Intramuscular progesterone.** The NICHD MFMU Network reported the results of a double-blind trial of 17 alpha-hydroxyprogesterone caproate (17P) for the prevention of spontaneous preterm birth in women with singleton pregnancies and a history of a prior spontaneous preterm birth. As compared to placebo, weekly intramuscular injections of 17P reduced the rate of preterm birth by approximately one-third. The American College of Obstetricians and Gynecologists (ACOG) recommends the use of 17P in patients with a prior *spontaneous* singleton (not medically indicated) preterm birth that occurred between 20 to 36 and 6/7 weeks, starting with weekly intramuscular injections of 250 mg between 16 and 20 weeks of gestation.
- 2. **Cerclage.** The use of cerclage to prevent recurrent preterm birth in women who had a prior spontaneous preterm at less than 34 weeks' gestation was investigated in a multicenter randomized trial. In this trial, 1,014 women underwent transvaginal sonography every 2 weeks between 16 and 23 weeks' gestation. In women whose cervical length was less than 25 mm, randomization occurred into two groups for no cerclage or placement of a McDonald cerclage. The primary outcome was the rate of preterm birth before 35 weeks' gestation. The rate of preterm birth in the no-cerclage group was higher (42% vs. 32%) but did not reach statistical significance ($p = 0.09$). However, in planned secondary analysis, there was significant reduction in the rate of preterm delivery in those patients who were randomized for a cervical length less than 15 mm. Currently, the American College of Obstetrics & Gynecology has not made a formal statement on the use of transvaginal cervical length ultrasound in the decision-making process for cerclage placement.
- 3. **Vaginal progesterone.** The majority of preterm births in the United States do not occur in women with a history of preterm birth. The use of progestational agents to prevent preterm

birth among women with risk factors OTHER than a previous preterm birth is an area of active research interest. Although one study showed that daily administration of vaginal progesterone significantly reduced the frequency of preterm birth before 34 weeks of gestation among asymptomatic women with a short cervix (less than 15 mm) as seen on ultrasonography. However, the routine use of progestational agents to prevent preterm birth among high-risk women is not proven and there are many unanswered questions with respect to the choice of agent, route of administration, dose, or even the clinical indication.

IV

EVALUATION OF PATIENTS IN PRETERM LABOR

A History Symptoms of preterm labor include:

1. Uterine cramping or contractions
2. Rhythmic low back pain
3. Pelvic pressure
4. Increased vaginal discharge
5. Vaginal bleeding (bloody show), which may result from cervical dilation

B Physical examination for women in possible preterm labor

1. A sterile **speculum examination** is part of the physical examination. The evaluation of fetal membrane status and the presence of cervicovaginal infection are determined at this time. If vaginal bleeding is present, an ultrasound must be performed to rule out placenta previa before a digital examination is performed.
 - a. Endocervical samples are obtained for gonorrhea and chlamydia testing if only an STD is suspected and if found should be treated. In addition, if the patient complains of a burning sensation, purulent discharge or erythema, a wet mount should be performed to evaluate for yeast, bacterial vaginosis, or trichomonas.
 - b. Group B streptococcus cultures are obtained if have not been done previously.
 - c. Premature rupture of membranes (PROM) is ruled out by doing fern and nitrazine tests.
2. **If there is no evidence of PROM**, a baseline **digital cervical examination** is performed, and follow-up examinations are warranted with continued uterine contractions.
3. A **urine specimen** is sent for culture. Pregnant women with asymptomatic bacteruria should be treated with antibiotics to reduce the risk of pyelonephritis, a serious disease if complicating. A Cochrane review of 14 randomized trials comparing antibiotic treatment with placebo or not treatment in pregnant women with asymptomatic bacteruria demonstrated that antibiotic treatment was effective in clearing asymptomatic bacteruria, reducing the incidence of pyelonephritis.
4. **Fetal heart rate** and **uterine activity monitoring** are used to assess fetal well-being and patterns of uterine contraction. Uterine contractions without cervical change may not constitute preterm labor.

C Diagnosis

1. Regular uterine contractions associated with progressive cervical change.
2. The goal is early identification of pregnant women who develop preterm labor and are at risk for delivery. Unfortunately this is a difficult task as the currently used techniques have only an average positive predictive value.
 - a. **Cervical length ultrasound.** This value can be measured accurately by a transvaginal ultrasound in a woman with an empty bladder. A cervical length of less than 25 mm in a patient with a *history* of preterm birth at less than 32 weeks has a positive predictive value of 55%. However, the clinical utility of this measurement is limited until effective treatment options are identified. There are insufficient data on the utility of cervical length in patients with ACTIVE preterm labor.
 - b. **Fetal fibronectin.** This extracellular matrix glycoprotein found in fetal membranes plays an active role in intercellular adhesion. Fibronectin found in the cervicovaginal fluid in the late second and early third trimesters has been associated with preterm birth. The positive predictive value of the fibronectin assay is approximately 25%. Fetal fibronectin testing may be useful in

women with symptoms and negative tests, as the negative predictive value is greater than 95%. This *may* avoid unnecessary treatment. However, the poor positive predictive value creates clinical ambiguity in patients who test positive. The most recent Cochrane review (2008) states that the review of five controlled studies that randomized 474 pregnant women did not find enough evidence to support or refute the use of the fetal fibronectin test for the management of women with symptoms of preterm labor.

V

MANAGEMENT OF PRETERM LABOR

A Tocolysis Treatment with tocolytic medications may not reduce the rate of preterm birth, but it may delay delivery for 48 hours and reduce the associated complications. The time gained allows for transfer to a tertiary center or corticosteroid administration. Women diagnosed with preterm labor at less than 34 weeks of gestation should be hospitalized and consideration given to the use of tocolytic medications.

1. Magnesium sulfate. This agent is currently the most commonly used tocolytic agent in the United States. Randomized controlled clinical trials suggest that it delays delivery by at least 48 hours.

a. The mechanism of action is that magnesium sulfate inhibits uterine contractility. Biochemically, magnesium acts by competitive inhibition of calcium at the motor end plate or the cell membrane, thereby decreasing calcium influx into the cell. It is cleared from the maternal circulation by the kidneys.

b. Administration involves infusing 2 to 4 g/hr to elevate serum levels to achieve uterine quiescence. The loading dose is 4 to 6 g given over 30 minutes. Once contractions cease, the infusion is reduced to the lowest possible dose to maintain uterine quiescence.

c. Precautions

- (1) Intravenous fluid is limited to 125 mL/hr, and fluid status is observed closely.
- (2) Deep tendon reflexes and vital signs should be checked hourly.
- (3) A pulmonary examination should be performed every 2 to 4 hours.
- (4) If signs of magnesium toxicity occur, the infusion should be discontinued and calcium gluconate or calcium carbonate administered as needed.

d. Complications

- (1) Nausea and vomiting
- (2) Flushing and headache
- (3) Muscle weakness
- (4) Pulmonary edema
- (5) Cardiopulmonary arrest

e. Contraindications to magnesium therapy include renal failure, myasthenia gravis, and hypocalcemia. In patients with cardiac and pulmonary disease, the effect of this tocolytic on existing pathologic conditions needs to be addressed and the risk/benefit ratio should be considered.

2. β -Mimetics

a. These agents stimulate β -receptors, leading to smooth muscle relaxation and decreased uterine contractions. However, given the significant side effects these agents are not used in the United States.

b. Ritodrine is the only agent approved by the Food and Drug Administration for the treatment of preterm labor. Because of its significant maternal side effects, it is not available in the United States.

c. Terbutaline is the other β -mimetic tocolytic agent, which may be given subcutaneously, parenterally, or orally. However, its parenteral use is limited by the significant side effects. When given orally, its use in the past has typically been in the setting of maintenance tocolysis; however, recent evidence shows that maintenance therapy does NOT reduce perinatal morbidity or mortality.

- (1) **Administration** is by three routes. The **subcutaneous dose** is 0.25 mg every 20 minutes three times and then every 4 hours; the **intravenous dose** is 0.125 mg every 4 hours; and the **oral dose** is 5 mg every 6 hours.

- (2) **Side effects** include tachycardia, palpitations, shortness of breath, pulmonary edema, hyperglycemia, hypokalemia, and tachyphylaxis.
 - (3) **Contraindications.** Relative contraindications to β -mimetic therapy are diabetes, certain cardiac diseases, and suspected abruption.
3. **Indomethacin.** This nonsteroidal anti-inflammatory medication inhibits the synthesis of prostaglandins (nonselective COX inhibitor), which are involved in the biochemical process of labor. A 2005 Cochrane review showed that compared with placebo, indomethacin use resulted in reduction in birth before 37 weeks' gestation, increase in gestational age at delivery, and increase in birth weight.
- a. Indomethacin, 50 to 100 mg, is initially given rectally. Remaining doses are given orally, 25 to 50 mg every 6 hours. This agent is usually given for no longer than 48 hours.
 - b. **Maternal side effects** include nausea, vomiting, and gastrointestinal bleeding.
 - c. A main **neonatal side effect** is **constriction of the ductus arteriosus**.
 - (1) Such constriction in a fetus causes tricuspid regurgitation and eventual right heart failure. Ductal constriction is usually transient and responds to discontinuation of the drug. Prior to 32 weeks' gestation, the incidence of ductal constriction is 5% to 10%. **From 32 to 35 weeks' gestation, the incidence of ductal constriction is 50%.**
 - (2) Because of this significant side effect, indomethacin is **uncommonly used as a tocolytic after 32 weeks' gestation**.
 - d. **Other significant neonatal complications** include oligohydramnios, pulmonary hypertension, and (possibly) necrotizing enterocolitis.
4. **Calcium channel blockers.** The most commonly studied calcium channel blocker in the setting of preterm labor has been nifedipine, which can be administered either orally or sublingually. This calcium channel blocker decreases smooth muscle contractions. Early studies comparing nifedipine to magnesium sulfate found similar efficacy between the medications; however, nifedipine tends to be associated with more side effects.
- a. Nifedipine is administered orally, 10 to 20 mg every 8 hours.
 - b. **Maternal side effects** include a decrease in blood pressure, tachycardia, and headache. Rarely, severe maternal hypotension following sublingual and oral nifedipine has been reported, resulting in nonreassuring fetal status and potentially fetal death.

B Contraindications to tocolytic therapy

- 1. Absolute
 - a. Severe preeclampsia and eclampsia
 - b. Nonreassuring fetal heart rate
 - c. Significant antepartum bleed
 - d. Clinical chorioamnionitis
- 2. Relative contraindications
 - a. Major fetal anomaly
 - b. Mild preeclampsia
 - c. Maternal cardiac disease

C **Refractory preterm labor** This condition is defined as persistent uterine contractions and cervical change despite maximal tocolytic therapy. Management may include **amniocentesis**, which can be performed to rule out an intra-amniotic infection. However, the prevalence of a positive test is low.

- 1. A Gram stain is positive for intra-amniotic infection if bacteria are present.
- 2. A glucose level of less than 14 mg/dL may be a sign of intra-amniotic infection.
- 3. A positive amniotic fluid culture signals intra-amniotic infection.

D Adjunctive therapy

- 1. **Corticosteroids**
 - a. Corticosteroids are given to women in preterm labor at 24 to 34 weeks' gestation. Repeated courses should not be done outside a research trial.

- b. This medication induces fetal lung maturity, and optimal benefit begins 24 hours after initiation of therapy. Corticosteroids accelerate pulmonary maturity by stimulating the synthesis and release of surfactant from type II pneumocytes.
 - c. Corticosteroids have been demonstrated to decrease mortality, respiratory distress syndrome, and intraventricular hemorrhage.
- 2. **Antibiotics.** These agents should only be given as prophylaxis for neonatal group B streptococcal infection.
 - a. Antibiotics are started on admission and continued if the group B streptococcus culture is positive. Affected women are treated for 7 days and then retreated during labor and delivery if the latency period is longer than 7 days.
 - b. Antibiotics are discontinued if the group B streptococcus culture is negative.
 - c. The use of antibiotics to *treat* preterm labor is ineffective and may be harmful.
 - d. Pregnant women with asymptomatic bacteruria should be treated with antibiotics to reduce the risk of preterm birth and pyelonephritis.
- 3. **Magnesium sulfate for cerebral palsy prevention.** A recent study investigated the use of magnesium sulfate to prevent cerebral palsy in women between 24 and 31 weeks' gestation at imminent risk for preterm delivery. Moderate or severe cerebral palsy occurred less frequently in the survivors of the magnesium sulfate group. Further studies are needed before this therapy should be incorporated into standard of care.
- 4. **Ineffective interventions.** Interventions that been demonstrated to be ineffective at preventing preterm birth include the treatment of asymptomatic genital tract infections (*Trichomonas*), the treatment of periodontal disease, home monitoring of uterine activity, bed rest with prolonged hospitalization, abstinence, or the use of maintenance or prophylactic tocolytic drugs outside of the immediate 48 hours used to obtain corticosteroid therapy in active preterm labor.

E Fetal assessment

- 1. **Ultrasound**
 - a. An ultrasound is performed on admission to assess the estimated fetal weight and fetal presentation.
 - (1) The estimated fetal weight can indicate whether the fetus has grown appropriately.
 - (2) The fetal presentation is important when making a delivery plan. A fetus in breech presentation usually requires a cesarean section.
- 2. **Fetal well-being.** The fetal heart rate testing should be reassuring before starting tocolytic therapy.

VI

PRETERM PREMATURE RUPTURE OF MEMBRANES

A Definition PPRM is rupture of fetal membranes prior to 37 weeks' gestation.

B Epidemiology

- 1. PPRM is responsible for 25% to 33% of all of preterm births each year.
- 2. Between 13% and 60% of patients with PPRM have an intra-amniotic infection.
- 3. Between 2% and 13% of patients with PPRM have postpartum endometritis.
- 4. The earlier the gestational age, the greater the potential for pregnancy prolongation; 75% of patients deliver within 1 week.

C Etiology

- 1. **Intrauterine infection is the major causal factor.**
- 2. Associated etiologic factors include low socioeconomic status, STDs, prior PPRM and preterm delivery, vaginal bleeding, cervical conization, tobacco smoking, uterine overdistention, and emergency cerclage.

D Evaluation A sterile **speculum examination** is performed to evaluate the fetal membrane status and to inspect the cervix.

- 1. Membrane rupture is confirmed by visualization of amniotic fluid in the posterior fornix or by passing of amniotic fluid from the cervical canal.

2. The vaginal pH is normally 4.5 to 6.0, and the pH of amniotic fluid is 7.1 to 7.3. Nitrazine paper turns blue with a pH above 6.0 to 6.5.
 - a. False-positive nitrazine tests result from semen, alkaline antiseptics, bacterial vaginosis, and blood.
 - b. Amniotic fluid from the vaginal pool produces a fernlike pattern on a microscope slide when allowed to dry.
 - c. If the patient's history is suggestive of PPROM but the sterile speculum examination is equivocal, an amniocentesis can be performed. Amniotic fluid can be sent for Gram stain and culture. In addition, dilute indigo carmine can be instilled into the amniotic fluid. A tampon is then placed in the patient's vagina. After a few hours it is removed. If the tampon is blue, PPROM has been confirmed. If the tampon is white, the patient does not have PPROM.
3. Once membrane rupture has been confirmed, **digital examination of the cervix should be avoided** until labor or induction of labor.
4. Endocervical samples may be considered for gonorrhea and chlamydia testing if clinically indicated.
5. Group B streptococcus cultures are obtained.
6. May consider sending a urine specimen for culture if clinically indicated.
7. Fetal heart rate and uterine activity monitoring are used to assess fetal well-being and uterine contraction pattern.
8. An ultrasound is performed on admission to assess the estimated fetal weight and fetal presentation.

E Management

1. In the absence of labor, chorioamnionitis, or nonreassuring fetal heart rate testing, patients with PPROM can be expectantly managed until 34 to 35 weeks' gestation with the following medications:
 - a. Corticosteroids. A complete course is given from 24 to 34 weeks' gestation.
 - b. Broad-spectrum antibiotics. A 7-day course (2 days intravenous, 5 days oral) is given. Antibiotics prolong the latency period and improve perinatal outcomes in patients with PPROM.
2. Fetal well-being is assessed daily with a nonstress test and a follow-up biophysical profile as needed.
3. Chorioamnionitis, labor, or nonreassuring fetal heart rate testing mandates delivery at any gestational age.



Study Questions for Chapter 15

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A 32-year-old woman, gravida 4, para 3, with a history of premature delivery in her last two pregnancies is seen in the outpatient office at 16 weeks' gestation. Her ultrasound shows a viable, singleton intrauterine pregnancy. She has no medical problems, has never had surgery, and has no known drug allergies. You counsel her about her high risk of a recurrent preterm birth. While discussing various options in an attempt to prevent this outcome, which of the following drug options is most recommended:

- ☐ A Penicillin therapy for group B streptococcus starting now
- ☐ B Azithromycin for prophylactic treatment of sexually transmitted infections
- ☐ C 17 alpha-hydroxyprogesterone caproate starting at 16 weeks' gestation
- ☐ D High-dose vitamin A therapy

2. A 24-year-old, gravida 2, para 1, female at 34 weeks of gestation presents to the labor floor with malaise, chills, and vomiting. Her temperature is 38.1°C, blood pressure 110/70 mm Hg, pulse is 100 beats/min, and her respirations are 18/min. She has acute fundal tenderness. Her cervical examination is 2 to 3 cm dilated, 40% effaced, and vertex at -1 station. Mild-to-moderate contractions are palpated and recorded every 5 to 10 minutes. Urinalysis shows no evidence of bacteria. On vaginal examination, membranes are ruptured. In addition to the administration of steroids, the most appropriate next step is:

- ☐ A Fetal fibronectin testing
- ☐ B Performance of a cervical length ultrasound
- ☐ C Treatment with magnesium sulfate for tocolysis
- ☐ D Administration of intravenous antibiotics and induction of labor

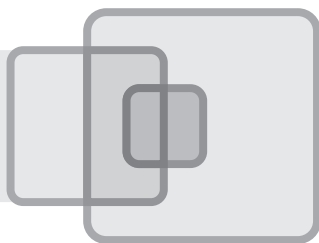
3. When compared to placebo inpatient tocolytic therapy in patients with preterm labor works to:

- ☐ A Prolong gestation by 3 weeks
- ☐ B Have no efficacy
- ☐ C Prolong gestation by 48 hours
- ☐ D Reduce the likelihood that the patient will deliver preterm



Answers and Explanations

1. **The answer is C.** The current ACOG guidelines recommend that all patients with a history of prior spontaneous preterm birth should be offered 17P starting between 16 and 20 weeks and continuing until delivery. Patients should be counseled about this option and referral to a maternal fetal medicine specialist regarding their poor obstetrical history can be offered. The use of antibiotics to treat group B streptococcus infection in the first trimester, prophylactic, and in the setting of a positive urine culture is contraindicated. The use of antibiotics for asymptomatic sexually transmitted infections is contraindicated. Vitamin A therapy is teratogenic in pregnancy.
2. **The answer is D.** This patient has chorioamnionitis given her high temperature and fundal tenderness. In the setting of ruptured membranes, this diagnosis is even more likely. Immediate antibiotics for chorioamnionitis therapy should be started, and consideration given to commencement of a labor induction or augmentation once the patient is stabilized.
3. **The answer is C.** The use of tocolysis is only for the immediate 48 hours to achieve betamethasone therapy. Treatment beyond this period has not found to be effective and may in fact be harmful.



Hypertension in Pregnancy

DOMINIC MARCHIANO

I

INTRODUCTION

Hypertensive disease complicates 8% to 11% of all pregnancies. It is the leading cause of maternal morbidity in developed countries (followed by obstetric hemorrhage and thromboembolism) and accounts for 15% of maternal deaths in the United States.

II

DEFINITIONS

A Chronic hypertension

1. Persistent **blood pressure greater than 140/90 mm Hg before the 20th week** of pregnancy
 - a. **Mild:** over 140/90 mm Hg
 - b. **Severe:** over 180/110 mm Hg
2. Hypertension initially diagnosed any time during pregnancy that persists for more than 12 weeks' postpartum

B Gestational hypertension (pregnancy-induced hypertension [PIH]). Definitions of hypertension based on **incremental increases** in blood pressure over baseline (e.g., diastolic blood pressure at 24 weeks, i.e., 15 mm Hg higher than a reading from before 20 weeks) are **no longer used to diagnose PIH**.

1. **Diagnostic criterion:** onset of hypertension after 20 weeks' gestation, without proteinuria
 - a. Absolute blood pressure of 140/90 mm Hg twice over 6 hours, without prior comparison
 - b. Absolute mean arterial pressure of 105 mm Hg without prior comparison
 - c. Blood pressure returns to normal by 12 weeks' postpartum

C Preeclampsia: gestational hypertension with proteinuria

1. **Proteinuria** is defined by 300 mg on a 24-hour collection. This usually correlates with 1+ on a dipstick, but random dipstick measurements require confirmation by 24-hour evaluation.
2. **Preeclampsia** may be **mild or severe** (Table 16–1). Criteria for **severe preeclampsia** suggest end-organ involvement (Table 16–2). After a **grand mal seizure**, preeclampsia is termed **eclampsia**.
3. **HELLP syndrome** (hemolysis, elevated liver enzymes, low platelets). This **variant of severe preeclampsia** develops in 10% of women with severe preeclampsia. However, approximately 10% of women with HELLP syndrome are normotensive, which is classified as atypical HELLP syndrome.
4. **Superimposed preeclampsia on chronic hypertension**
 - a. New-onset proteinuria after 20 weeks in a woman with chronic hypertension
 - b. Sudden increase in proteinuria, edema, or blood pressure or a platelet count less than 100,000/mm³ in a woman with chronic hypertension and proteinuria before 20 weeks' gestation

III

CHRONIC HYPERTENSION

A Effects on mother

1. Mild chronic hypertension is unlikely to adversely affect pregnancy. Pregnancy is unlikely to hasten the progression of maternal hypertensive end-organ disease.
2. Morbidity is increased over de novo preeclampsia.

TABLE 16–1 Hypertensive Disorders During Pregnancy: Indications of Severity

Abnormality	Mild	Severe
Diastolic blood pressure	<100 mm Hg	>110 mm Hg
Proteinuria	Trace to +1	Persistent 2+ or more
Headache	Absent	Present
Visual disturbance	Absent	Present
Upper abdominal pain	Absent	Present
Oliguria	Absent	Present
Convulsion	Absent	Present (eclampsia)
Serum creatinine	Normal	Elevated
Thrombocytopenia	Absent	Present
Liver enzyme elevation	Minimal	Marked
Fetal growth restriction	Absent	Obvious
Pulmonary edema	Absent	Present

Reprinted with permission from Cunningham FG, MacDonald PC, Gant NF. Williams Obstetrics. 21st Ed. New York: McGraw-Hill, 2001:570, Table 24–2.

B Effects on fetus

1. **Abruptio placentae** are four to eight times more likely in pregnancies complicated by chronic hypertension.
2. When preeclampsia is superimposed on chronic hypertension, preeclampsia occurs earlier and is associated with more pronounced **decreases in uteroplacental perfusion**. Intrauterine growth retardation (IUGR) may result from decreased uteroplacental perfusion.
 - a. However, IUGR is not more frequent in cases of mild chronic hypertension without superimposed preeclampsia.
 - b. When preeclampsia is superimposed on chronic hypertension, the incidence of IUGR is 30% to 40%.
3. **Prematurity is more common** with severe chronic hypertension.
4. **Perinatal mortality** approaches 25% in severe chronic hypertension.

C Antihypertensive management

1. Treatment reduces the risk of maternal morbidity. Whether it reduces perinatal morbidity and mortality remains controversial.
2. Existing antihypertensive therapy should be continued on diagnosis of pregnancy.
3. **Antihypertensive agents**

TABLE 16–2 Criteria for Severe Preeclampsia

Systolic hypertension >160 mm Hg
Diastolic hypertension >110 mm Hg
Proteinuria >5 g/24 hr
Oliguria <500 mL/24 hr
Cerebral or visual disturbances
Epigastric pain
Pulmonary edema
Evidence of microangiopathic hemolysis
Hepatocellular dysfunction
Thrombocytopenia
Intrauterine growth restriction
Oligohydramnios

- a. **α -Methyldopa** is used frequently and has been studied the most. There is **no evidence of fetal or maternal adverse events**.
- b. **Labetalol** (α - and β -blockade) is associated with a possible increase in growth restriction.
- c. **Nifedipine** has limited data, but it rapidly reduces blood pressure.
- d. **β -Antagonists** have been associated with low birth weight.
- e. **Angiotensin-converting enzyme inhibitors are contraindicated** in pregnancy because of adverse effects on fetal renal function.

D Antepartum management

1. **Baseline evaluation for end-organ disease**
 - a. Renal function tests
 - b. Ophthalmologic examination
 - c. Electrocardiogram
2. Antihypertensive therapy is unlikely to benefit a pregnancy complicated by mild hypertension. It should be reserved for pregnancies complicated by moderate or severe hypertension (diastolic blood pressure more than 100 to 110 mm Hg), where it reduces the incidence of cardiovascular and cerebrovascular events.
3. Ultrasound should be used to determine specific gestational age. Serial ultrasound surveillance should be performed from 28 weeks through delivery for surveillance for IUGR.
4. Nonstress testing and amniotic fluid assessment should be started at 32 to 34 weeks' gestation.
5. Labor induction by 40 weeks' gestation can be considered.

IV

PREECLAMPSIA: EPIDEMIOLOGY

A **Rate of occurrence** 7% of pregnancies, excluding the first-trimester losses

B **Risk factors**

1. **Pregnancy history.** Primigravidas constitute 65% of cases.
 - a. Multiple gestation: 30% incidence
 - b. Gestational trophoblastic disease: 70% incidence
2. **Maternal age.** Preeclampsia occurs at extremes of maternal age. However, the association with young age is confounded by the association with primigravity. However, **maternal age of more than 40 years** is an independent risk factor.
3. **Family history.** Evidence for a genetic contribution includes a 37% incidence in sisters and a 26% incidence in daughters. This pattern is consistent with a dominant gene with reduced penetrance.
4. **Obesity.** Incidence is directly related to degree of obesity.
5. **Chronic hypertension.** Preeclampsia occurs in approximately 25% of women with chronic hypertension.

V

PREECLAMPSIA: PATHOPHYSIOLOGY

A **Pathophysiologic changes**

1. **Cardiovascular system**
 - a. Cardiac output remains normal, and increased total peripheral vascular resistance accounts for the hypertension.
 - b. Preeclamptic endothelial cells generate less prostacyclin, a vasodilator, than normal endothelial cells. Less prostacyclin allows greater vascular sensitivity to angiotensin II, thus promoting vasospasm and increasing peripheral vascular resistance.
2. **Coagulation system**
 - a. Disseminated intravascular coagulation occurs in 10% of patients with preeclampsia.
 - b. Because of endothelial damage, most of these patients have mild procoagulant consumption and elevated fibrin degradation products.
 - c. Diffuse intravascular coagulation may arise from vascular damage sustained during vasospasm.

3. Renal function

a. Glomerular changes

- (1) Glomerular filtration rate (GFR) is usually decreased in preeclampsia. Decreased renal plasma flow and **glomeruloendotheliosis**, which occludes the capillary lumen, account for the lower GFR.
- (2) Protein leaks into urine. The glomerulus, which is normally impermeable to large proteins, becomes more permeable. In part, glomerular damage results from both vasospasm and endothelial damage. This leakage exceeds the tubules' ability to reabsorb proteins.

b. Tubular changes, which affect the clearance of uric acid

- (1) Uric acid is normally completely filtered at the glomerulus, secreted, and mostly reabsorbed by the proximal tubules.
- (2) Uric acid clearance is 10% of creatinine clearance.
- (3) Decreased uric acid clearance is observed prior to a GFR disturbance, suggesting a tubal etiology in which the mechanism remains unknown.
- (4) Increased production by hypoxic tissues contributes to increased serum uric acid.

c. Renin–angiotensin–aldosterone system

- (1) Levels of the following components are increased:
 - (a) Plasma renin activity and plasma renin concentration
 - (b) Angiotensinogen
 - (c) Angiotensin II
 - (d) Aldosterone
- (2) The theory that the renin–angiotensin system mediates the pathophysiologic alterations of preeclampsia is suggested by three factors:
 - (a) Potent vasoconstrictor effect of angiotensin II
 - (b) Stimulation of aldosterone by angiotensin II and consequent sodium retention
 - (c) The finding that large doses of angiotensin II can cause proteinuria
- (3) It is possible that, despite decreased intravascular volume, preeclamptic vasoconstriction results in a physiologic perception of overfill, which suppresses renin release.

4. Other signs of end-organ disease

- a. Visual disturbances result from papilledema and suggest cerebral involvement.
- b. Epigastric pain suggests hepatocellular dysfunction and edema and liver capsule distention.
- c. IUGR and oligohydramnios suggest placental vasculopathy and uteroplacental insufficiency.

B Pathologic findings

1. Liver

- a. Initially, arteriolar vasodilation results in hemorrhage into the hepatocellular columns. This condition is found on liver biopsy in 66% of patients with eclampsia.
- b. Hepatic infarction occurs later and is found on liver biopsy in 40% of patients with eclampsia.

2. Kidney

- a. **Glomerular endotheliosis** is the characteristic renal lesion of preeclampsia.
 - (1) Endothelial cells enlarge and may occlude the capillary lumen.
 - (2) Podocytes are not altered.
 - (3) Changes are completely reversible with resolution of preeclampsia.
- b. Nonglomerular changes such as tubular alterations are less common.

3. Placenta and placental site

- a. The syncytiotrophoblast is abnormal, containing areas of cell death and degeneration, syncytial knots, and decreased density of microvilli
- b. Cytotrophoblastic cells proliferate in placental villi
- c. Placental vascular pathology
 - (1) In normal pregnancy, the spiral artery endothelium, elastic lamina, and smooth muscle are replaced by trophoblast. This creates a low-resistance, high-flow system. These changes affect both the decidual and myometrial vessels.
 - (2) In preeclampsia, these changes do not uniformly occur or are limited to decidual vessels.
 - (3) These observations can be made on the first-trimester abortion specimens, suggesting that pathologic change precedes the clinical presentation.

VI**PREECLAMPSIA: CLINICAL MANIFESTATIONS****A Clinical signs**

1. **Hypertension** is required for diagnosis.
2. **Edema** is related to sodium retention, and is not limited to dependent edema.
3. **Hyperreflexia** is common.

B Laboratory findings

1. **Renal function**
 - a. Proteinuria
 - b. Hyperuricemia is likely caused by both altered renal function and increased production of uric acid
 - c. Increased serum creatinine is inversely correlated with creatinine clearance
2. **Hematology findings**
 - a. Hemoconcentration as reflected by an increased hematocrit
 - b. Thrombocytopenia
3. **Hepatic findings.** Increased transaminases, when associated with microangiopathic hemolysis and coagulopathy, suggest HELLP syndrome.

VII**PREECLAMPSIA: MANAGEMENT**

A Delivery is the only known treatment. At term (37 weeks' gestation), delivery is recommended.

B Route of delivery

1. **Vaginal delivery is preferable** to cesarean delivery, which should be reserved for the usual obstetric indications.
2. Cesarean delivery may be preferred in cases of severe preeclampsia remote from term with an unfavorable cervix.
3. Some evidence suggests that preeclampsia may expedite cervical ripening and labor induction.

C Antepartum treatment (before 37 weeks)

1. **Mild preeclampsia** may be managed expectantly using the following interventions. It is controversial whether in- or outpatient management is preferable.
 - a. Bed rest
 - b. Blood pressure and urinary protein monitoring
 - c. Twice-weekly nonstress tests
 - d. Laboratory surveillance
2. **Stable severe preeclampsia**
 - a. **Before 24 weeks.** Pregnancy termination should be offered.
 - b. **Before 32 weeks.** Delivery is always a legitimate course of action, but expectant management with blood pressure control is an option.
 - (1) Expectant management requires intensive fetal and maternal surveillance.
 - (2) Antenatal corticosteroids are recommended.
 - (3) Delivery is mandatory if the patient develops thrombocytopenia, abnormal liver function tests, uncontrollable hypertension, pulmonary edema, oligohydramnios, or abnormal fetal testing.
 - (4) Presence of proteinuria or controllable hypertension does not require immediate delivery.
 - c. **After 32 weeks.** Delivery is appropriate after documentation of fetal lung maturity.
 - (1) If fetal lung maturity is negative, antenatal steroids should be given before 34 weeks.
 - (2) Alternatively, steroids can be given to all patients between 32 and 34 weeks. Delivery may be effected 48 hours later without documenting fetal lung maturity.
 - (3) **Unstable severe preeclampsia.** Treatment **at any gestational age** involves prompt delivery.

TABLE 16–3 Effects of Magnesium at Different Serum Levels

Effect	Level (mEq/L)
Seizure prophylaxis	4–6
Loss of deep tendon reflexes	10
Respiratory depression	15
General anesthesia	15
Cardiac arrest	25

D Intrapartum management

1. **Seizure prophylaxis.** Because there are no signs that accurately predict seizures, **prophylaxis is most effective if all women with preeclampsia are treated.**
 - a. **Magnesium sulfate** is superior to other antiepileptic medications for preventing eclampsia-related seizures and seizure-related morbidity and mortality.
 - (1) An intravenous loading dose of 4 to 6 g is usually followed by a maintenance infusion of 2 to 4 g/hr.
 - (2) Patients must be monitored for signs of magnesium toxicity, such as hyporeflexia and respiratory depression.
 - (3) Magnesium toxicity may be confirmed by testing serum levels (Table 16–3). It can be reversed with 1 g of calcium gluconate.
 - (4) In instances in which magnesium sulfate cannot be used (e.g., myasthenia gravis, end-stage renal disease [because of impaired magnesium clearance]), phenytoin is safe.
2. **Antihypertensive therapy**
 - a. **Indications**
 - (1) **Therapy should be considered for:**
 - (a) Persistent diastolic blood pressure of over 100 to 110 mm Hg
 - (b) **Persistent systolic blood pressure of over 150 to 160 mm Hg**
 - (2) **Therapy is certainly indicated for** systolic blood pressure of over 180 mm Hg or diastolic blood pressure of over 110 mm Hg.
 - b. **Pharmacologic agents**
 - (1) **Hydralazine** (preferred agent) reduces afterload but compensates by increasing heart rate; therefore, uterine perfusion is not usually compromised.
 - (2) **Labetalol** does not reduce afterload.
 - c. **Invasive cardiac monitoring** should be considered in the presence of oliguria or pulmonary edema.
3. **Type of anesthesia**
 - a. **Epidural anesthesia** is safe for patients with normal clotting ability and no thrombocytopenia. It can be used for either vaginal or cesarean deliveries.
 - b. **General anesthesia** should be used with caution because the stimulation of intubation may exacerbate hypertension.

E Postpartum management

1. Magnesium sulfate should be continued for 24 hours but may be discontinued earlier in the presence of pronounced diuresis, because therapeutic levels are not likely attainable.
2. Indications for acute antihypertensive therapy are the same as for the antepartum or intrapartum period.
3. Women who continue to have hypertension but have a persistent diastolic blood pressure of less than 100 mm Hg may be discharged on oral therapy.
4. PIH usually disappears completely by 2 weeks postpartum.

VIII**PREECLAMPSIA: PREVENTION**

There is no reliable method for preventing preeclampsia. Low-dose aspirin, calcium, antioxidants, low-sodium diet, and fish oil have all been shown to be ineffective.

IX**ECLAMPSIA**

Eclampsia is preeclampsia complicated by generalized tonic–clonic seizures. Pathophysiology of the convulsions is unknown.

- A** May occur before, during, or after labor and delivery
- B** May cause maternal death
- C** Consider cerebral imaging, especially if the seizures occur more than 24 hours postpartum
- D** **Treatment** includes **magnesium sulfate** to control seizures; **antihypertensive therapy** with hydralazine, labetalol, or nifedipine; **prevention** of aspiration and hypoxia; and **delivery** when the mother is stabilized

X**PREECLAMPSIA: PROGNOSIS**

With **timely delivery and magnesium sulfate**, the maternal mortality rate should be virtually zero.

- A** **Recurrence** The risk is 40% for severe preeclampsia and increases with earlier diagnosis of the index case.
- B** **Future hypertension** Preeclampsia does not accelerate hypertension but seems to unmask existing, yet undiagnosed, chronic hypertension.
 1. Women with preeclampsia in a first pregnancy are no more likely to develop hypertension than controls.
 2. Multiparous women are more likely to develop hypertension, but this is confounded because preeclampsia is unlikely to develop de novo in multiparas. Many of these women had underlying hypertension.



Study Questions for Chapter 16

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. You have been seeing a 21-year-old woman, gravida 1, para 0, at 28 weeks of gestation, throughout her pregnancy. She has no known medical history. She denies blurry vision, epigastric or right upper quadrant pain, severe headache, or trouble breathing. Her blood pressure and urine protein dipstick results for the past three visits are as follows: visit 1, BP = 105/60, U_{dip} = 0; visit 2, BP = 110/65, U_{dip} = 1+; visit 3, BP = 142/80, U_{dip} = 1+. Today, her BP = 120/75 and U_{dip} = trace. She reports lots of fetal movement. Her fundus measures 25 cm. Lungs are clear to auscultation bilaterally. Deep tendon reflexes are 2+ symmetric. Results from laboratory studies you sent on visit 3 are the following:

Platelet count = 130,000/ μ l
 Leukocytes = 10,400/ μ l
 Peripheral blood smear = no hemolysis
 Aspartate aminotransferase = 340 U/L
 Alanine aminotransferase = 200 U/L
 Blood urea nitrogen = 12 mg/dL
 Creatinine = 0.6 mg/dL
 Uric acid = 6.0 mg/dL
 Glucose = 105 mg/dL

The most accurate diagnosis for this patient is:

- ☐ A Chronic hypertension
- ☐ B Gestational hypertension
- ☐ C Mild preeclampsia
- ☐ D Severe preeclampsia
- ☐ E Superimposed preeclampsia on chronic hypertension

2. The diagnosis of preeclampsia would be advanced to eclampsia if the woman in Question 1 developed which of the following?

- ☐ A Severe, unremitting headache
- ☐ B Platelet count of 50,000/ μ l
- ☐ C Grand mal seizures
- ☐ D Blood pressure 180/120 mm Hg
- ☐ E Visual scotomata

3. A 23-year-old primigravid woman at 37 weeks of gestation (confirmed by a first-trimester ultrasound) presents to the clinic for routine prenatal care. She reports active fetal movement and abdominal pain. Her blood pressure is 162/103 initially and she has 2+ protein on the urine dipstick. Her physical examination is unremarkable except for diffuse tenderness on the abdomen; however, there is no rebound tenderness. Her fundus measures 36 cm above the symphysis pubis. You send her to labor and delivery where a complete blood cell count, liver enzymes, electrolytes, uric acid, urinalysis, and coagulation profile are drawn. On labor and delivery, her blood pressure is 166/104 and there is 3+ proteinuria on urine dipstick. Her cervix is closed, long, firm, and posterior and fetal vertex is high. What is the next step in management?

- ☐ A Prostaglandin analog
- ☐ B Oxytocin
- ☐ C Magnesium sulfate
- ☐ D Methyldopa
- ☐ E Hydralazine

4. A 24-year-old primigravida at 35 weeks' gestation complains of mild headache and facial edema. Her blood pressure is 160/100 and her reflexes are brisk. You suspect that she has preeclampsia. Her urinalysis is likely to show which of the following?

- ☐ A Proteinuria
- ☐ B Hematuria
- ☐ C Glycosuria
- ☐ D Ketonuria
- ☐ E Leukocytes

QUESTIONS 5–6

Directions: The response options for Questions 5 and 6 are the same. For each clinical scenario, select the most appropriate management option.

- ☐ A Immediate cesarean section
- ☐ B Induction of labor
- ☐ C Admission to hospital for observation
- ☐ D Outpatient observation

5. A 38-year-old African American woman, gravida 1, presents for a routine visit at 39 weeks' gestation. Her blood pressure is persistently 140/90 mm Hg, and her urine protein is +2. Physical examination is otherwise unremarkable, and she is completely asymptomatic. Her cervix is 2 cm dilated and 90% effaced, with the fetal vertex at 0 station.

6. A 25-year-old Asian woman, gravida 2, para 0, presents at 33 weeks' gestation for a routine visit. Her blood pressure is 150/100 mm Hg, and her urine protein is +3. Physical examination is otherwise unremarkable. She reports mild headache (relieved with acetaminophen), but no right upper quadrant pain or visual scotomata.

7. A 26-year-old nurse, gravida 2, para 1, at 32 weeks of gestation, presents to labor and delivery (L&D) because of elevated blood pressures. She says her systolic blood pressures have been in the high 170s and her diastolic blood pressures have been in the low 110s. She denies abdominal pain, visual disturbances, or severe headache. Her blood pressure at L&D is 150/98 and she has 1+ proteinuria. You send off appropriate labs, admit the patient to the hospital, and keep her on bed rest. Which of the following is an appropriate next step in management?

- ☐ A Induce labor—vaginal delivery
- ☐ B Cesarean section
- ☐ C Phenytoin
- ☐ D Labetalol
- ☐ E Betamethasone

8. A 35-year-old woman, gravida 5, para 1, at 6 weeks of gestation, is seeing you because she just found out she is pregnant. She has a 6-year history of essential hypertension controlled on a diuretic agent. After you perform a routine prenatal examination, you change her blood pressure medication to methyldopa and ask her to use it throughout the entire pregnancy. Which of the following is the best reason for using methyldopa in a patient with chronic hypertension during pregnancy?

- ☐ A It is the best antihypertensive during pregnancy
- ☐ B It decreases the risk of IUGR in the fetus
- ☐ C It decreases the risk of abruptio placentae
- ☐ D It decreases the risk of maternal end-organ damage
- ☐ E It increases uteroplacental perfusion

9. Which of the following is an independent risk factor for PIH?

- ☐ A Multiparity
- ☐ B Family history of chronic hypertension
- ☐ C Age older than 40 years
- ☐ D Age younger than 20 years
- ☐ E History of seizure disorder

10. Which of the following might be found in a patient with MILD preeclampsia?

- ☐ A Oligohydramnios
- ☐ B Proteinuria in excess of 3 g/24 hr
- ☐ C Thrombocytopenia
- ☐ D Intrauterine growth restriction
- ☐ E Elevated transaminases



Answers and Explanations

1. **The answer is D** [II C and Table 16–1]. Although this patient has normal blood pressures and only mild proteinuria, her blood pressure measurements have been rising steadily over the last few visits. This is the opposite of what happens in normal pregnancy. The most important feature that makes this clinical scenario “severe” is the elevated liver enzymes. Both aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are more than three times normal. [Note: You should have a sense of normal and abnormal laboratory values for common electrolytes, liver enzymes, and cell counts. Exact values may vary between laboratories.] This patient has severe preeclampsia, and the clinician should send the patient to the hospital for admission. Chronic hypertension is defined as blood pressure greater than 140/90 before Week 20 of pregnancy or hypertension that is diagnosed at any time during pregnancy and persists for more than 12 weeks’ postpartum. HELLP syndrome is a variant of severe preeclampsia.

2. **The answer is C** [II B 2 b]. Eclampsia is a subset of PIH that is defined by the occurrence of grand mal, otherwise known as tonic–clonic seizures. Symptoms and signs of impending neurologic instability may include headache, visual changes, hyperreflexia, or clonus, but eclampsia is defined only when a grand mal seizure occurs. Blood pressure higher than 160/110 signifies severe preeclampsia. Low platelet count is a sign of HELLP syndrome, not eclampsia.

3. **The answer is C** [VII A and VII E 1]. This clinical scenario is describing severe preeclampsia based on her elevated systolic blood pressure (greater than 160 mm Hg) and persistent elevated proteinuria (greater than or equal to 2+). She also has abdominal pain, which is a sign of severe preeclampsia. The first step would be to put her on magnesium sulfate for seizure prophylaxis. It may sound counterintuitive to place someone on magnesium (which is also a tocolytic agent) while attempting to deliver. However, in the management of preeclampsia, magnesium sulfate is used for seizure prophylaxis. Remember, delivery is the only true cure for preeclampsia, so the next step would be to plan for her delivery. A prostaglandin analog can then be used as her Bishop score is low. Using oxytocin to induce this patient would be unsuccessful because her cervix is unfavorable (low Bishop score). Methyldopa is used for patients with chronic hypertension during pregnancy. Hydralazine is used for persistently high diastolic blood pressure, usually diastolic of over 105 mm Hg.

4. **The answer is A** [II B 2]. Proteinuria is characteristic of the urine of patients with preeclampsia, a form of PIH. PIH, a multiorgan system disease, commonly involves the cardiovascular, renal, neurologic, and hematologic systems. When renal involvement leads to proteinuria, the disease is called preeclampsia. Blood, glucose, or ketones are not commonly seen in the urine of preeclamptic women, unless other conditions are present.

5. **The answer is B** [III A 1; VII D 1 b]; 6. **The answer is C** [VII B 2 a to c; V D 1 a (1) to (4)]. The first patient has a diagnosis of mild PIH at term. Because she has proteinuria, her condition may be further classified as preeclampsia. The indicated treatment of PIH of any severity at term is delivery. Because her cervix is favorable, induction of labor is the preferred method of delivery. Induction may be initiated with intravenous oxytocin, and parenteral magnesium sulfate should be used for seizure prophylaxis.

The second patient presents with a more difficult problem because she is preterm. Her hypertension and proteinuria suggest that she has mild preeclampsia, but at this time, she does not satisfy the criteria for severe disease. With mild disease in a preterm patient, observation and evaluation for severe disease are indicated. Because of the serious complications that can occur, the patient is best managed in the hospital until sufficient evaluation to exclude severe PIH is completed. If further evaluation reveals severe disease, delivery is indicated.

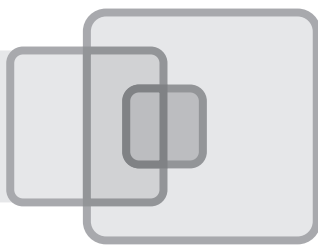
7. **The answer is E** [VII C 1 and C 2 c (1)]. According to criteria discussed in this chapter, this patient represents mild preeclampsia. Management of this case is more complicated because she is preterm (32 weeks). Because definitive management of preeclampsia is delivery, you must weigh the risks of

premature delivery for the fetus against the benefits of delivery to the mother. Mild preeclampsia may be managed expectantly (by bed rest, blood pressure and urine protein monitoring, twice-weekly non-stress testing, and lab evaluations) before 37 weeks of gestation. The best course of action (given the above answer choices) is to give antenatal steroids to try to effect fetal lung maturity. Delivery by cesarean section or vaginal birth is not appropriate in someone less than 37 weeks with mild preeclampsia. Anyone who has the diagnosis of preeclampsia needs to be on seizure prophylaxis. The best agent is magnesium sulfate, not phenytoin. Labetalol is used to treat persistently elevated diastolic blood pressure of over 105 mm Hg.

8. The answer is D [III C 1]. Treatment of hypertension during pregnancy reduces the risk of **maternal** morbidity probably by preventing end-organ damage. Whether therapy reduces perinatal morbidity and mortality remains controversial. Methyldopa is the most commonly used antihypertensive medication, but it is not necessarily the best. There is evidence that labetalol is as good, if not better, than methyldopa during pregnancy. Methyldopa does not increase uteroplacental perfusion.

9. The answer is C [IV B 2]. While the association of maternal age younger than 20 years with preeclampsia is confounded by primigravity, maternal age greater than 40 years is an independent risk factor for preeclampsia. Personal history of chronic hypertension would be associated with a 25% risk for the development of preeclampsia, but a family history of chronic hypertension does not similarly increase the risk. Seizure disorder and multiparity are not related to preeclampsia.

10. The answer is B [Tables 16–1 and 16–2]. Oligohydramnios, thrombocytopenia, intrauterine growth restriction, and transaminitis are criteria for severe preeclampsia. Proteinuria of 5 g in a 24-hour specimen is also a criterion for severe preeclampsia. However, proteinuria of only 3 g would be insufficient for this diagnosis.



Other Medical Complications of Pregnancy

HARISH M. SEHDEV

I

DIABETES

Diabetes affects 2% to 3% of all pregnancies. Of those, approximately 90% are cases of **gestational diabetes**, which is diabetes whose onset occurs during pregnancy.

A Effect of pregnancy on glucose metabolism

1. **Maternal metabolism adjusts** to provide nutrition for both the fetus and the mother.
 - a. Increased insulin secretion occurs as a result of β -cell hyperplasia from the increased levels of estrogen and progesterone.
 - b. Insulin antagonism results from the increase in human somatomammotropin (produced by syncytiotrophoblasts).
 - c. Increased insulin degradation by placental insulinase occurs.
2. A more than 40% **decrease in insulin sensitivity** normally occurs by late in pregnancy, and maintenance of glucose homeostasis results from exaggeration in both the rate and amount of insulin release.
3. Therefore, as pregnancy progresses, women with marginal pancreatic reserve may be unable to meet insulin demands, especially in late pregnancy, and those with preexisting diabetes will need more insulin.
4. **Fetal glucose levels are directly proportional to maternal glucose concentrations.**
 - a. Insulin **does not cross** the placenta.
 - b. After delivery, insulin requirements for patients with underlying diabetes **decrease** because of the decrease in estrogen, progesterone, placental insulinase, and human somatomammotropin.

B **Effects of preexisting diabetes on pregnancy** Before the use of insulin therapy, complications of diabetes for both the mother and the fetus **were** extremely high. Although insulin therapy has lowered the risk of complications, pregnancies in women with diabetes are still associated with an increased risk of adverse events.

1. **Maternal complications**
 - a. Preeclampsia and eclampsia
 - b. Diabetic ketoacidosis
 - c. Worsening preexisting nephropathy
 - d. Worsening preexisting retinopathy
 - e. Infection
 - f. Polyhydramnios
 - g. Cesarean delivery
 - h. Postpartum hemorrhage
 - i. Mortality
2. **Fetal complications**
 - a. Miscarriage
 - b. Unexplained stillbirth

- c. **Perinatal mortality** of approximately 2% to 5% (significantly lower than the risk of approximately 65% before insulin therapy)
- d. **Congenital malformations**, which account for up to 50% of associated perinatal mortality. Anomalies can affect most organ systems, in particular anencephaly and spina bifida in the **central nervous system**, ventricular septal defects and situs inversus in the **cardiac system**, and a characteristic embryopathy called sacral agenesis or **caudal regression**. These usually occur by **7 weeks' gestation** (see Chapters 6 and 7)
- e. Abnormal fetal intrauterine growth (both macrosomia and growth restriction)
- f. Neonatal complications, including respiratory distress syndrome, hypoglycemia, hypocalcemia, polycythemia, and hyperbilirubinemia

C Management of patients with diabetes

1. **Prior to conception.** Appropriate prenatal care for women with **preexisting diabetes** should begin before conception. Such care may decrease the risk of congenital malformations.
 - a. Adjust insulin to normalize glucose levels. **Goals** for pregnancy are different than for non-pregnant individuals and are as follows: fasting glucose values **less than 95 mg/dL** and 2-hour postprandial values less than **120 mg/dL**.
 - b. Order **hemoglobin A1C** to assess glycemic control. HgB A1C should be less than 6% prior to pregnancy.
 - c. Provide **folic acid** supplementation.
 - d. Provide nutrition counseling.
2. **First trimester**
 - a. Obtain ultrasound between 6 and 8 weeks' gestation if possible for accurate dating.
 - b. Order **hemoglobin A1C** to assess glycemic control (the risk for congenital abnormalities increases with higher hemoglobin A1C values).
 - c. Assess overall health for effects of background vascular involvement (e.g., renal, ophthalmologic, or cardiac).
 - d. **Multiple** daily injections of insulin (or an insulin pump) may be needed to maintain glucose in the range described above.
3. **Second trimester: screening for malformations**
 - a. Maternal serum α -fetoprotein (AFP) screening at 15 to 20 weeks to assess the risk for fetal neural tube abnormalities
 - b. Ultrasound at 16 to 20 weeks to evaluate fetal anatomy
 - c. Fetal echocardiography at 20 to 22 weeks to help screen for fetal cardiac abnormalities
4. **Third trimester: assessment of fetal well-being**
 - a. Surveillance of fetal well-being should begin at **28 weeks** with maternal fetal activity assessment (kick counts) because the risk of unexplained stillbirth is increased. **Nonstress testing or biophysical profiles** should begin at 32 weeks or earlier if significant maternal vascular disease exists or there is evidence of fetal growth restriction.
 - b. Ultrasound every 4 to 6 weeks to assess fetal growth.
5. **Timing of delivery.** The time at which delivery occurs depends on both maternal glycemic control and the health and maturity of the fetus.
 - a. In patients with good glycemic control and reassuring fetal testing, the physician can wait for the onset of labor until 40 weeks' gestation.
 - b. If induction of labor is considered before 39 weeks, assessment of fetal lung maturity by amniocentesis should be performed to assess the lecithin-to-sphingomyelin (**L/S**) ratio and the presence of **phosphatidylglycerol** in the amniotic fluid. If testing does not reveal an L/S ratio of at least 2:1 or the presence of phosphatidylglycerol, delivery should be delayed until repeat testing confirms fetal lung maturity, or after 39 weeks as long as fetal testing remains reassuring. Other tests for fetal lung maturity on amniotic fluid are available.
6. **Method of delivery.** The mode of delivery should be individualized. In patients with diabetes, the fetus can weigh in excess of 4,000 g, which increases the risk of **shoulder dystocia** (entrapment of the shoulder after delivery of the head). However, many cases still occur in fetuses that weigh less than 4,000 g. Ultrasound assessment of fetal weight is helpful but not completely accurate.

- a. If the suspected weight of the fetus does not exceed 4,000 g, vaginal delivery (including induction of labor) can be attempted.
- b. If the suspected weight of the fetus exceeds 4,000 g (macrosomia), elective cesarean delivery can be offered.
- c. For all deliveries, euglycemia should be maintained and ketosis avoided.

D **Gestational diabetes** is defined as diabetes whose onset occurs during pregnancy and is attributed to the pregnancy. Women with gestational diabetes are at increased risk for developing overt diabetes later in life.

1. Effect of gestational diabetes on pregnancy

- a. Increased risk of macrosomia
- b. Increased risk of preeclampsia
- c. Increased rate of stillbirth if fasting glucose is elevated
- d. **Fetal anomalies are not increased** (unless diagnosis is made early in pregnancy and patient in reality has overt diabetes)

2. Screening for gestational diabetes may be needed on the basis of the following **risk factors**:

- a. Strong family history
- b. Persistent glucosuria
- c. History of unexplained stillbirth or miscarriage
- d. Prior macrosomic fetus
- e. Obesity
- f. Age older than 25 years

3. Universal screening is recommended because selective screening may miss up to 50% of cases of gestational diabetes.

- a. The **1-hour glucose tolerance test** consists of a 50-g glucose load. There is no set abnormal value, and the threshold value may be 130, 135, or 140 mg/dL. The lower the threshold, the greater the screen positive rate with a greater sensitivity. An abnormal value requires a standard glucose tolerance test.
- b. The **standard glucose tolerance test is a 3-hour test** consisting of a 100-g glucose load and four serum glucose determinations. Gestational diabetes is diagnosed if there are at least two abnormal values.
 - (1) Fasting value: 95 mg/dL
 - (2) 1-hour value: 180 mg/dL
 - (3) 2-hour value: 155 mg/dL
 - (4) 3-hour value: 140 mg/dL

4. Management

- a. Provide nutritional counseling and dietary adjustment. If the disease can be controlled by diet alone, patients can be followed similarly to those without diabetes. No evidence supports early delivery.
- b. Monitor fasting and 2-hour postprandial glucose values.
- c. Give insulin if fasting glucose values are greater than 95 mg/dL and 2-hour postprandial values are greater than 120 mg/dL.
- d. Oral hypoglycemics such as glyburide can also be used. If Glyburide fails to control sugars, treat with insulin.
- e. Patients who require medications or are unable to maintain glycemic control should be followed similarly to patients with preexisting diabetes.

5. Follow-up. After the postpartum visit, patients with gestational diabetes should be screened routinely for diabetes.

II

THYROID DISEASE

Thyroid disease affects up to 1% of all pregnancies.

A **Effects of pregnancy on thyroid function**

- 1. Plasma inorganic iodine concentration decreases because of increased renal excretion and increased glomerular filtration.

2. Enlargement of the thyroid gland occurs.
3. Serum thyroxine (T_4)-binding globulin is increased.
4. Laboratory assessment of thyroid function is altered.
 - a. Increased total T_4
 - b. Increased total triiodothyronine (T_3)
 - c. Increased radioiodine uptake
 - d. Decreased T_3 resin uptake
 - e. Unchanged free T_4 , free T_3 , and thyroid-stimulating hormone (TSH) levels

B Hyperthyroidism This condition occurs in approximately 1 in 200 pregnancies.

1. **Effects on pregnancy.** The signs and symptoms of normal pregnancy can mimic signs of hyperthyroidism. If hyperthyroidism is untreated, the risk of complications (e.g., preeclampsia, preterm delivery, congestive heart disease, and adverse perinatal outcome) is increased. Pregnant patients with hyperthyroidism should have third-trimester antepartum testing as part of obstetrical care.
2. **Causes**
 - a. **Graves disease**, an autoimmune process, is the most common cause. This condition is associated with an increase in thyroid-stimulating antibodies that stimulate the TSH receptors. These antibodies can cross the placenta, resulting in fetal thyrotoxicosis.
 - b. **Gestational trophoblastic disease** (see Chapter 39) should be considered, especially if hyperthyroidism occurs early in gestation, and a pelvic ultrasound should be ordered.
3. **Diagnosis**
 - a. Tachycardia
 - b. Thyromegaly
 - c. Exophthalmos
 - d. Poor maternal weight gain
 - e. Severe hyperemesis gravidarum
 - f. Onycholysis (separation of nail from the nail bed)
 - g. Decreased TSH with increased free T_4
4. **Management.** Therapy can be either medical or surgical with minimal risk to mother and fetus.
 - a. **Medical therapy**
 - (1) **Propylthiouracil (PTU)** prevents both the synthesis of thyroid hormone in the thyroid gland and the peripheral conversion of T_4 to T_3 . The drug readily crosses the placenta and may induce **fetal hypothyroidism** and goiter, although this is rare. The goal of treatment is to maintain a maternal high-normal level of free T_4 .
 - (2) **Methimazole** prevents only the release of thyroid hormone and has been associated with **aplasia cutis**, a reversible developmental disorder of the fetal scalp. This drug should not be used in pregnancy.
 - (3) Beta-blockers may be used to control tachycardia associated with hyperthyroidism.
 - (4) **Radioactive iodine is contraindicated** in pregnancy because it crosses the placenta and can ablate the fetal thyroid gland.
 - b. **Surgical therapy.** In cases that are refractory to medical therapy, thyroidectomy may be necessary.
5. **Thyroid storm** is a rare complication of hyperthyroidism that can be associated with heart failure. Treatment includes propylthiouracil, potassium iodide, beta-blockers, hydration, and control of body temperature.

C Hypothyroidism

1. **Effects on pregnancy**
 - a. Associated with the first-trimester miscarriages
 - b. Increased risk of preeclampsia, abruptio placentae, stillbirth, and intrauterine growth restriction (IUGR)
 - c. Infants of untreated women with significantly increased TSH levels may be at risk for **decreased performance on IQ tests**.
2. **Diagnosis.** Increased TSH and decreased free T_4 are the basis of diagnosis.

3. **Management.** Hypothyroidism is treated with supplemental thyroid hormone. Thyroid hormone replacement dose should be increased in the first trimester. No need for the third-trimester antepartum testing. Infants of treated mothers are healthy.

III

URINARY TRACT INFECTION

Women are at greater risk for urinary tract infections during pregnancy because of the anatomic and physiologic changes that occur with pregnancy. **A urine culture should be obtained in all women at their first prenatal visit**, and urine dipstick analysis should be performed at all subsequent visits.

A Asymptomatic bacteriuria This condition is defined as the presence of bacteria within the urinary tract without symptoms.

1. Asymptomatic bacteriuria is present in 5% to 10% of all pregnant women. The incidence is highest in black multiparas with sickle cell trait.
2. **Treatment** requires administration of an antibiotic (e.g., ampicillin or nitrofurantoin) to which the causal organism is sensitive.
3. **Consequences of lack of treatment**
 - a. Pyelonephritis in up to 40% of affected women
 - b. Risk factor for low birth weight
4. A **follow-up culture** is necessary after treatment has been completed.

B Acute urethritis

1. Usually, the **etiologic agents** are *Escherichia coli*, *Chlamydia trachomatis*, and *Neisseria gonorrhoeae*.
2. **Signs and symptoms** include frequency, dysuria, and urgency. Mucopurulent discharge from the urethra may be present.
3. **Urinalysis** reveals white blood cells without bacteria.
4. **Urine culture** and urethral culture for gonorrhea and chlamydia should be performed.
5. **Treatment** is based on the causal agent.

C Cystitis

1. **Etiologic agents**
 - a. The most common pathogen is *E. coli* (80% to 90% of cases).
 - b. Other causal pathogens include *Klebsiella pneumoniae*, *Proteus* species, and Gram-positive organisms such as enterococci and group B streptococci.
2. **Symptoms** include frequency, urgency, suprapubic pain, dysuria, and hesitancy. Hematuria may be present. Fever is uncommon.
3. **Diagnosis** is made by using a clean catch specimen or one obtained by midstream urine collection or bladder catheterization.
4. **Treatment** involves a short course of antibiotics to which the organism is sensitive. Inadequate treatment may lead to pyelonephritis.
5. A **follow-up culture** is necessary after treatment is complete.

D Acute pyelonephritis This condition affects 1% to 2% of all pregnancies. It usually results from lower tract infection. Up to 90% of cases are unilateral and usually affect the right side.

1. **Predisposing factors unique to pregnancy**
 - a. Ureteral compression at the pelvic brim caused by the enlarging uterus
 - b. Decreased tone and peristalsis of the ureters resulting from increased progesterone levels
 - c. Decreased bladder sensitivity, which may result in overdistention and the need for catheterization
2. The **most common causative agent** is *E. coli*.
3. **Signs and symptoms** may include:
 - a. Fever, chills, and back pain
 - b. Nausea or vomiting

- c. Anorexia
- d. Preterm contractions and preterm labor
- 4. **Complications** may include:
 - a. Bacteremia and septic shock
 - b. Pulmonary edema and respiratory distress syndrome
 - c. Renal dysfunction
 - d. Preterm labor
 - e. Chorioamnionitis
- 5. **Treatment**
 - a. Inpatient therapy is preferred.
 - b. Hydration is useful.
 - c. Intravenous antibiotics are used until the patient is afebrile for 24 to 48 hours; they are followed by oral antibiotics with appropriate sensitivity to complete a 7- to 10-day course of treatment.
 - d. Lack of response to treatment should prompt radiologic evaluation for an abscess or renal calculi.
 - e. Follow-up therapy includes daily antibiotic suppression for the remainder of the pregnancy.
 - f. Up to 30% of patients may develop recurrent urinary tract infections during pregnancy.

IV

ANEMIA

Anemia has been defined by the Centers for Disease Control and Prevention as a hemoglobin concentration of less than 11 g/dL in the first and third trimester of pregnancy and less than 10.5 g/dL in the second trimester. Anemia is broadly classified as acquired or hereditary.

A Acquired anemias

1. **Iron-deficiency anemia.** The most common cause of anemia in pregnancy is **iron deficiency**. The iron requirements of pregnancy are considerable, and most women enter pregnancy with low iron stores.
 - a. In pregnancy, a woman needs an additional 1,000 mg of elemental iron.
 - (1) 300 mg goes to the fetus.
 - (2) 500 mg is used to expand the maternal red cell mass.
 - (3) 200 mg is shed through the gut and skin.
 - b. The level of **hematocrit naturally decreases** during the second trimester of pregnancy, because of the greater expansion of maternal plasma volume compared with the increase in red cell mass and hemoglobin mass.
 - c. Late in pregnancy, hemoglobin mass continues to increase while plasma volume remains steady.
 - d. Because of the normal transfer of iron from the mother to the fetus, the **fetus does not suffer from iron-deficiency anemia**.
 - e. While maternal absorption of iron is increased in pregnancy, treatment involves additional daily elemental iron (200 mg in divided doses) to correct the anemia and maintain adequate stores.
2. **Megaloblastic anemia.** This condition, which is rare in the United States, is characterized by impaired DNA synthesis. It occurs in pregnant women who consume neither fresh vegetables nor foods with a high content of animal protein.
 - a. **Folic acid deficiency** is the most common form.
 - b. Many women also have iron deficiency.
 - c. **Vitamin B₁₂ deficiency is rare** but should be checked for in women with a gastrectomy, Crohn's disease, or ileal resection.
 - d. Ethanol consumption may be a contributing factor.
 - e. Symptoms and signs of megaloblastic anemia during pregnancy include nausea, vomiting, and anorexia.
 - f. Treatment includes a well-balanced diet, oral iron, and folic acid (1 mg/d).

B Hereditary anemias, which are characterized by the hemoglobinopathies, result in increases in maternal morbidity and mortality, spontaneous abortion, and perinatal mortality.

1. **Sickle cell anemia** (hemoglobin SS disease; SS disease). This condition occurs when an individual receives the gene for the production of hemoglobin S, an abnormal variant of hemoglobin, from both parents.
 - a. The incidence of sickle cell trait in black adults is 1 in 12; therefore, the theoretical incidence of SS disease is 1 in 576 in the United States. The actual incidence in pregnant women is somewhat lower because of the higher mortality rate in individuals with SS disease. Pregnancy poses an increased risk of adverse outcome for both mother and fetus.
 - b. Infectious complications, such as pyelonephritis, cholecystitis, pneumonia, and skin infections, are increased in SS disease.
 - c. Complications of pregnancy increase. These include:
 - (1) Spontaneous abortion
 - (2) Preeclampsia
 - (3) Preterm labor and delivery
 - (4) IUGR
 - (5) Unexplained fetal demise
 - d. The number of **vaso-occlusive** crises increases in pregnancy. Treatment includes:
 - (1) Hydration
 - (2) Analgesics
 - (3) Oxygen
 - (4) Transfusion
 - (5) Screening and therapy for infections
 - e. Treatment during pregnancy includes:
 - (1) Screening and treatment of asymptomatic bacteriuria
 - (2) Urine culture every trimester
 - (3) Pneumococcal vaccine (recommended)
 - (4) Serial ultrasound to assess fetal growth
 - (5) Antepartum fetal surveillance
 - (6) Folic acid supplementation
 - f. Treatment during labor includes:
 - (1) Adequate hydration and oxygen to prevent sickling
 - (2) Analgesia
 - (3) Packed red blood cell transfusion if a cesarean section is considered and the hemoglobin level is very low
 - g. Although prophylactic transfusions may decrease the number of vaso-occlusive crises, they do not improve perinatal outcome.
2. **Sickle cell–hemoglobin C disease** (SC disease). Hemoglobin C, like hemoglobin S, results from a change in the sixth position of the β -chain and may be seen in patients of West African or Sicilian descent.
 - a. The incidence in the United States is 1 in 823 adult African Americans.
 - b. This disease is associated with less morbidity than SS disease but still carries an increased risk of pregnancy loss and pregnancy-induced hypertension.
 - c. Affected patients may experience pain crises that are marked by splenic sequestration and that can be associated with thrombocytopenia.
 - d. Treatment and follow-up are the same as that for patients with SS disease. The resulting anemia may require transfusion; such treatment is uncommon in the nonpregnant state.
3. **Sickle cell– β -thalassemia disease**. This condition has a perinatal mortality and morbidity rate similar to that of SC disease, with somewhat less maternal morbidity and mortality.
4. **Sickle cell trait** is inheritance of the gene for the production of hemoglobin S from one parent and hemoglobin A from the other. This condition occurs in 8.5% of African Americans, and it occurs in individuals of Mediterranean, Caribbean, Latin American, North African, Indian, and Southeast Asian descent.
 - a. The anemia in most patients is only mild.
 - b. Sickle cell trait does not appear to increase the risk of miscarriage, stillbirth, IUGR, or pregnancy-induced hypertension.

- c. There is an **increased risk for asymptomatic bacteriuria and urinary tract infections**. Therefore, women with the trait should have frequent urine cultures during pregnancy.
 - d. Paternal testing may be important because prenatal diagnosis of SS disease is available.
5. **Thalassemias.** The normal adult hemoglobins are A, A₂, and F. Ninety-five percent of adult hemoglobin is hemoglobin A (made by two α -chains and two β -chains). Most individuals also have small amounts of hemoglobin A₂ (two α -chains and two Δ -chains). The remainder is made up of hemoglobin F (two α -chains and two γ -chains). Patients with thalassemias have a **microcytic anemia** that can be found on their screening complete blood count.
- a. **α -Thalassemia.** The α -thalassemias are characterized by a deletion of one or more of the four genes from the α -chain.
 - (1) Deletion of one α -gene does not cause anemia.
 - (2) Deletion of two genes causes α -thalassemia trait, characterized by mild anemia.
 - (3) Deletion of three genes (hemoglobin H) causes moderate anemia; transfusion or splenectomy is rare.
 - (4) Deletion of four genes (Bart hemoglobin) causes severe intrauterine anemia with fetal hydrops and death, as well as maternal preeclampsia and postpartum hemorrhage.
 - b. **β -Thalassemia.** The β -thalassemias occur because of point mutations in the genes for β -chain production, leading to a decrease in β -chain formation. This decrease leads to a decrease in hemoglobin A production and a relative increase in the percentage of hemoglobin A₂ (more than 4%), which is evident on hemoglobin electrophoresis.
 - (1) β -Thalassemia trait occurs when β -globin production is decreased by 50%, causing a mild anemia with hypochromic microcytosis and occasional hepatosplenomegaly.
 - (2) β -Thalassemia intermedia occurs when production is decreased by 75%, leading to moderate anemia with occasional need for transfusion, hepatosplenomegaly, and iron overload.
 - (3) β -Thalassemia major occurs with no production of the β -chain, causing severe anemia, transfusion dependency, iron overload, bone deformities, and death in early adulthood. (Fetuses and newborns with β -thalassemia are not anemic because of the presence of hemoglobin F.)
 - c. Women with the most severe forms of β -thalassemia are transfusion dependent and require close supervision during pregnancy. During pregnancy, women with β -thalassemia intermedia may experience a drop in hemoglobin and hematocrit levels. The red blood cell mass does not expand normally because of deficient hemoglobin production.
 - (1) Folic acid supplementation is recommended to keep up with the accelerated red blood cell turnover.
 - (2) Iron therapy is indicated only for patients with demonstrable iron deficiency because of the risk of iron overload and hepatotoxicity.
 - (3) Pregnancy is well tolerated in patients with α - or β -thalassemia trait.
 - (4) Paternal testing may be important because **prenatal diagnosis is available**.

V

HEART DISEASE

A Incidence of heart disease in pregnancy

1. Approximately **1% of pregnancies are complicated by maternal heart disease**. Today, fewer women are seen with heart disease because of the decreased incidence of rheumatic fever and rheumatic heart disease. However, because of advances in corrective heart surgery, more women with congenital cardiac abnormalities reach childbearing age.
2. Women with severe heart disease are **at greater risk for pregnancy complications**:
 - a. Miscarriage
 - b. IUGR
 - c. Preterm delivery
 - d. Intrauterine demise
3. **Maternal mortality** with pregnancy depends on the specific lesion. All women with cardiac disease should seek preconceptual counseling with cardiac and perinatal specialists.

- a. The **highest risk** (maternal mortality as high as 50%) is associated with **pulmonary hypertension**, Marfan syndrome with aortic involvement, Turner syndrome with aortic involvement, complicated coarctation of the aorta, and Eisenmenger syndrome.
- b. The **lowest risk** (less than 1%) is associated with corrected tetralogy of Fallot, small atrial and ventricular septal defects, and patent ductus arteriosus.

B Diagnosis of heart disease during pregnancy

1. **Changes associated with normal pregnancy that may place an extra burden on women with heart disease include:**
 - a. **Expansion of plasma volume by as much as 50%**
 - b. **Increased cardiac output** (30% to 50%)
 - c. **Drop in systemic vascular resistance** up to 28 weeks' gestation
 - d. **Changes specific to labor**
 - (1) Pain, which can increase heart rate and blood pressure
 - (2) Shift into the intravascular compartment of as much as 500 mL of plasma with each uterine contraction
 - (3) Regional anesthesia, which can decrease cardiac output and blood pressure
 - (4) Postpartum increase in blood volume and cardiac output by 10% to 20%. Initially, cardiac output and blood pressure may fall after delivery
2. **Symptoms of normal pregnancy that can be confused with symptoms of heart disease**
 - a. Functional systolic murmurs
 - b. Fatigue, dyspnea, and palpitations
 - c. Edema, especially in the lower extremities
 - d. Enlarged cardiac silhouette on chest radiograph
3. **Signs and symptoms that should lead to suspicion of heart disease**
 - a. Progressive limitation of physical activity
 - b. Chest pain
 - c. Syncope with exertion
 - d. Severe dyspnea
 - e. Diastolic murmur
 - f. Loud systolic murmur
 - g. Cyanosis or clubbing
 - h. Abnormal heart rhythm on electrocardiography
 - i. Abnormal echocardiography

C Management

1. **Preconception**
 - a. Counseling about risks
 - b. Reviewing current medical regimen
2. **During pregnancy**
 - a. Close follow-up with a cardiologist
 - b. Frequent maternal echocardiography
 - c. Fetal echocardiography at 20 to 22 weeks' gestation (A woman with a congenital cardiac abnormality is at greater risk for having a fetus with a congenital cardiac lesion.)
 - d. Careful evaluation of any change in maternal symptoms
 - e. Evaluation and treatment for infection and anemia, which could worsen the maternal condition
 - f. Anticoagulation, with heparin if appropriate
 - g. Hospitalization for signs of deterioration
3. **In labor and postpartum**
 - a. Team management, involving cardiology, anesthesiology, and nursing
 - b. Invasive monitoring, if necessary
 - c. Antibiotic prophylaxis, if necessary
 - d. Avoidance of rapid changes in blood pressure and heart rate
 - e. **Forceps or vacuum-assisted** delivery in some cases to avoid prolonged second stage of labor
 - f. Continued close observation in the postpartum period

VI

PULMONARY DISEASE

A Physiologic changes associated with pregnancy

1. **Mechanical changes of chest cavity**
 - a. Upward displacement of diaphragm (as much as 4 cm)
 - b. Increase in transverse diameter of chest (2 cm)
 - c. Increase in chest circumference (5 to 7 cm)
 - d. Increased diaphragmatic excursion
 - e. Increase in subcostal angle
2. **Changes in pulmonary function**
 - a. Increased tidal volume (30% to 40%)
 - b. Decrease in expiratory reserve
 - c. Increase in minute ventilation
 - d. Decreased lung volume caused by displacement of diaphragm (Total lung volume decreases 5%, and residual volume decreases 20%.)
 - e. No change in forced expiratory volume in 1 second

B Dyspnea of pregnancy As many as 70% of pregnant women report dyspnea, and the etiology is not understood. Physical examination should be unremarkable.

C Asthma This condition complicates approximately 4% to 8% of all pregnancies and worsens in about one-third of cases. According to the National Asthma Education and Prevention Program, for pregnant women with asthma, “it is safer ... to be treated with asthma medications than it is for them to have symptoms and exacerbations.” Evaluation of asthma in pregnancy includes pulmonary function tests and self-assessment.

1. **Pregnancy complications**
 - a. If asthma is poorly controlled, it may be associated with increased risk of preterm delivery, IUGR, preeclampsia, cesarean delivery, and both perinatal and maternal morbidity and mortality. Ultrasound assessment for fetal growth and antepartum testing should be part of the third-trimester management in patients with severe asthma.
 - b. Use of steroids can be associated with increased risk of gestational diabetes and postpartum hemorrhage.
2. **Goal of treatment.** To maintain adequate fetal oxygenation by preventing maternal hypoxic episodes.
3. **Treatment.** Medications are divided into rescue therapy or long-term medications.
 - a. **β-Agonists.** Short acting (inhaled albuterol) is the primary treatment for acute exacerbations. Long acting forms used as add on therapy with inhaled corticosteroids.
 - (1) No increase in the incidence of congenital malformations.
 - (2) Side effects include tachyphylaxis and arrhythmias.
 - b. **Glucocorticoids**
 - (1) Inhaled for chronic therapy. Increased dose with increased severity of disease
 - (2) Intravenous and oral therapy for acute exacerbations
 - (3) Safe in pregnancy
 - c. **Alternative add-on therapies:**
 - (1) Aminophylline:
 - (a) **Crosses the placenta** and has no demonstrable effects on the fetus.
 - (b) Levels must be adjusted in pregnancy.
 - (c) Narrow therapeutic index and side effects are common and include nausea, tachycardia, and arrhythmias.
 - (2) Leukotriene receptor agonists
 - (a) Safe to use in pregnancy
 - d. **Additional therapy**
 - (1) Avoid allergens
 - (2) Education for self-monitoring and use of medications
4. **Status asthmaticus.** Provide immediate treatment using the following interventions:
 - a. Oxygenation
 - b. Hydration

- c. Subcutaneous catecholamines
- d. Intravenous steroids
- e. Nebulized β -agonists
- f. Intubation, if necessary

D Pneumonia In addition to being life-threatening to the mother when severe, pneumonia is also associated with preterm birth. Chest radiography during pregnancy can be accomplished with little radiation exposure to the fetus using lead shielding to the mother's abdomen.

1. ***Streptococcus pneumoniae***: most common bacterial pathogen
 - a. Associated with **smoking**
 - b. **Sudden onset** is characteristic. **Signs and symptoms** include:
 - (1) Tachypnea
 - (2) Fever
 - (3) Shaking chills
 - (4) Productive cough
 - (5) Purulent sputum
 - c. **Diagnosis**
 - (1) Lobar consolidation on chest radiograph
 - (2) Sputum culture and Gram stain
 - (3) Blood culture
 - d. **Treatment**
 - (1) Hospitalization
 - (2) Intravenous penicillin followed by oral penicillin for 10 to 14 days
2. **Other pathogens that cause pneumonia**
 - a. ***Mycoplasma pneumoniae***
 - (1) Common in young adults
 - (2) Slow onset of symptoms with nonproductive cough
 - (3) Clinical diagnosis, with a chest radiograph that reveals patchy infiltrates
 - (4) Not responsive to penicillin and should be treated with erythromycin
 - b. ***Klebsiella pneumoniae* and *Haemophilus influenza***
 - (1) Usually occurs in heavy smokers, alcoholics, and immunocompromised patients
 - (2) Requires immediate hospitalization and appropriate antibiotics
 - c. **Influenza A**
 - (1) Characterized by sparse sputum production and interstitial infiltrates
 - (2) Usually self-limited but can be complicated by secondary bacterial pneumonia
 - d. **Varicella** (chickenpox)
 - (1) Has mortality as high as 30%. The risk of pneumonia with primary varicella infection increases in smokers and in pregnant women in the third trimester.
 - (2) Requires treatment with intravenous acyclovir. Varicella-zoster immune globulin can be given as prophylaxis to a susceptible woman exposed to the virus.
 - (3) The **varicella vaccine** is a live virus and is **contraindicated** in pregnancy. Varicella titers should be checked prior to pregnancy and if the patient is nonimmune, she can be vaccinated, however, the patient should be aware of that vaccination involves two injections given a month apart so attempts at pregnancy is delayed 2 months.

E Sarcoidosis The etiology of this granulomatous disease is unknown. Sarcoidosis can affect many organ systems.

1. Most commonly, affected individuals are 20 to 40 years of age.
2. The condition is most commonly diagnosed by evidence of **bilateral hilar adenopathy** on routine chest radiography. Definitive diagnosis is made by histology.
3. Most patients are asymptomatic and require no treatment. If therapy is necessary, glucocorticoids are the primary treatment.
4. Pregnancy has no long-term side effects. Sarcoidosis does not appear to affect pregnancy outcome adversely. **Most patients improve** as the pregnancy progresses.

5. In pregnant women, it is necessary to assess renal and hepatic involvement and test pulmonary function.

F Tuberculosis This condition, which is caused by *Mycobacterium tuberculosis*, is unfortunately becoming more common because of HIV infection and increasing immigration from developing countries. Congenital tuberculosis is rare, and most cases of perinatal infection result from horizontal transmission.

1. **Symptoms**

- a. Lethargy
- b. Cough
- c. Dyspnea
- d. Night sweats

2. **Diagnosis**

- a. Skin testing with subcutaneous dose of intermediate-strength purified protein derivative (PPD)
- b. Chest radiograph
- c. Culture and identification of acid-fast bacilli or fluorescent stain of sputum

3. **Treatment.** The risk of adverse outcome in pregnancy does not appear to increase if treatment is adequate. Therapy has become more complex with the emergence of resistant strains of *M. tuberculosis*.

- a. **Isoniazid** for 9 months: standard therapy

- (1) Side effects: peripheral neuropathy, toxic hepatitis (especially if older than 35 years)
- (2) Prophylactic use in recent PPD converters without active disease

- b. **Ethambutol:** added for resistant strains

- (1) Safe in pregnancy
- (2) Side effect with higher doses: optic neuritis in the mother

- c. **Streptomycin**

- (1) Avoid in pregnancy
- (2) Associated with damage to cranial nerve VIII and renal damage in fetus

- d. **Rifampin**

- (1) Avoid in pregnancy, crosses the placenta
- (2) May increase the risk of congenital malformations

VII

THROMBOEMBOLIC DISEASE

A Epidemiology and etiology

1. Thromboembolic disease is **the leading cause of death in pregnant and postpartum women.**
2. Thromboembolic disease occurs in 0.02% to 0.3% of pregnant patients and in 0.1% to 1.0% of postpartum patients.
3. Untreated deep vein thrombosis (DVT) in pregnancy causes pulmonary embolism (PE) in as many as 24% of patients.
 - a. The mortality rate is 15%.
 - b. If patients are treated adequately, the risk of PE is 4.5%, with a risk of mortality of less than 1%.
4. Most cases of thromboembolic disease in pregnancy are associated with a hereditary thrombotic disorder. These disorders may also be associated with an increased risk for adverse pregnancy outcome in the second and third trimester (early-onset preeclampsia, early-onset IUGR, unexplained stillbirth, and placental abruption). The risk of thromboembolic disease increases significantly with the presence of more than one of the following abnormalities:
 - a. Factor V Leiden mutation
 - b. Prothrombin mutation
 - c. Antiphospholipid antibody
 - d. Protein C or protein S deficiency
 - e. Antithrombin III deficiency

B Pathophysiology

1. Pregnancy is a hypercoagulable state. Increased estrogen production is associated with increases in clotting factors.
2. The gravid uterus may compress the inferior vena cava and pelvic veins, causing venous stasis.

C Diagnosis**1. Deep vein thrombosis****a. Signs and symptoms**

- (1) Calf pain
- (2) Palpable cord
- (3) Tenderness
- (4) Unilateral edema of the leg
- (5) Homans' sign
- (6) Dilated superficial veins

b. Real-time ultrasonography with duplex and color Doppler ultrasound is the **procedure of choice** to detect proximal DVT. Although it is highly sensitive and specific for femoral and popliteal thrombosis, real-time ultrasonography **does not detect pelvic vein thrombosis**, which may be responsible for pulmonary embolism.

c. Venography. This procedure is considered the gold standard for diagnosis of DVT.

- (1) Radiation is minimal, and the fetus can be protected by abdominal shielding.
- (2) This procedure is invasive and expensive.
- (3) **This procedure should not be performed in patients who are at risk of having a contrast allergy.**

d. ^{125}I radioisotope scanning should **not** be used in pregnancy.

e. Impedance plethysmography is safe, but its sensitivity and specificity have not been well studied in pregnancy.

2. Pulmonary embolism**a. Clinical findings**

- (1) Tachypnea
- (2) Dyspnea
- (3) Pleuritic pain
- (4) Apprehension
- (5) Cough
- (6) Tachycardia
- (7) Hemoptysis

b. Arterial blood gas analysis

- (1) A PaO_2 of more than 80 mm Hg on room air makes the diagnosis unlikely. If signs and symptoms persist, further evaluation is recommended.
- (2) An increased alveolar–arterial gradient may indicate PE.

c. Ventilation–perfusion scan. This should not be performed in pregnancy.

- (1) Most patients with a PE have an abnormal ventilation–perfusion scan (sensitivity, 98%).
- (2) Many patients without emboli also have an abnormal scan (specificity, 10%).
- (3) The degree of abnormality is graded low, intermediate, or high probability, with further intervention and therapy guided by clinical suspicion.

d. Pulmonary angiogram. This technique is the gold standard for diagnosis of PE.

- (1) It is indicated for anticoagulation failures when caval interruption is considered, to distinguish between recurrent embolization and fragmentation of the original clot.
- (2) It is associated with minimal risk to the fetus.

e. Spiral computed tomography (CT) scan. This test is now the first-line test for PE and is replacing the angiogram as the gold standard, but it may miss small emboli. However, accuracy for small vessel emboli is improving with technology and thinner CT sections. CT can evaluate for other etiologies for patient's symptoms.

D Management**1. Deep vein thrombosis**

- a. Bed rest with extremity elevation
- b. Therapeutic anticoagulation with heparin or subcutaneous injections of low-molecular-weight heparin. Both forms of heparin **do not cross the placenta** and are safe when breastfeeding.
- c. **Warfarin** is a known **teratogen** and should be avoided in pregnancy. It may be used postpartum, even if the mother is nursing.

2. Pulmonary embolism

- a. Oxygen to maintain maternal PaO₂ more than 70 mm Hg
- b. Bed rest for 5 to 7 days
- c. Therapeutic anticoagulation with heparin until 3 to 6 months postpartum

E Management of women who have experienced a prior thromboembolic event The management of women with a prior history of a DVT or PE is controversial. Evaluation for a hereditary and acquired thrombotic abnormality should be pursued, and consideration should be made for prophylactic anticoagulation with either heparin or low-molecular-weight heparin.

VIII**SEIZURE DISORDERS**

Seizure disorders affect approximately 1% of the population and 1 in 200 pregnancies. Fifteen percent of these cases result from infection, injury, intracranial processes, and metabolic disorders. The remaining 85% are idiopathic (no inciting incident or etiology). Patients with seizure disorders may have reduced fertility.

A Effects of pregnancy on seizure disorders

- 1. Seizure activity may increase. Increased seizure activity can be controlled with appropriate medication and compliance.
- 2. Pregnancy can affect medication levels.

B Effects of seizure disorders on pregnancy

- 1. **Maternal complications.** No increase in the risk of maternal complications usually results.
- 2. **Fetal complications**
 - a. Increased risk of stillbirth
 - b. Decreased birth weight
 - c. Increased risk of epilepsy in life
 - d. Increased risk of hemorrhagic complications in newborns exposed to anticonvulsants in utero
 - e. Increased risk of congenital abnormalities
 - (1) Anticonvulsants are associated with increased risk. For pregnant women taking anti-epileptic medications, data are being collected by the Antiepileptic Drug Registry (888 233-2334)
 - (a) Carbamazepine: neural tube defects, craniofacial defects, and nail hypoplasia
 - (b) Phenytoin: microcephaly, dysmorphic facies
 - (c) Trimethadione: multiple malformations and mental retardation
 - (d) Valproic acid: neural tube defects
 - (e) As of this time, newer medications such as lamotrigine and levetiracetam have not been associated with any specific constellation of findings and patients should be encouraged to enroll in the registry
 - (2) The risk increases with the number of anticonvulsants used in the first trimester.
 - (3) It is unclear whether a maternal seizure disorder itself may be a risk factor for fetal anomalies.

C Management of pregnant women with a seizure disorder**1. Preconception**

- a. If the patient is seizure free, consider stopping medications under supervision of a neurologist.
- b. Monotherapy should be used, if possible.
- c. Folic acid supplementation may decrease risk of neural tube abnormalities.

2. During pregnancy

- a. Early ultrasound to establish correct gestational age
- b. Monitoring of medication levels
- c. Compliance with medication regimen
- d. Second-trimester screening for congenital abnormalities, including maternal serum AFP, ultrasound, and fetal echocardiography
- e. Serial ultrasound examinations to check for fetal growth restriction
- f. Vitamin K supplementation late in the third trimester (controversial)

IX**RH ISOIMMUNIZATION****A Definitions**

1. **Isoimmunization (sensitization)** is caused by maternal antibody production in response to exposure to red blood cell antigens. If these antibodies are directed against fetal red cell antigens, the antibodies can cross the placenta and cause fetal hemolytic disease.
2. **Rh isoimmunization**, a leading cause of hemolytic disease, specifically refers to antibodies against the Rh group, C, c, E, e, and D (the most commonly encountered). Rh antigens are present on fetal cells by the 38th day postconception.

B Epidemiology

1. Approximately 1% of all pregnancies are complicated by red blood cell sensitization. The incidence of Rh isoimmunization in the United States has fallen since the 1960s because of anti-D immune globulin.
2. Fifteen percent of Caucasians, 5% to 8% of African Americans, and 1% of Native Americans and Asians are Rh negative (absence of D antigen).

C Criteria (all factors must be present in an Rh-negative pregnant woman)

1. The fetus must be Rh positive.
2. Enough fetal cells must reach the maternal circulation (fetomaternal bleed).
3. The mother must make antibody to D antigen.
 - a. Some women are immunogenic nonresponders (as many as 30%).
 - b. ABO incompatibility with the fetus can be protective.
 - c. The amount of antigen necessary to generate an immune response with anti-D antibody is different for each woman.

D Prevention of Rh isoimmunization (anti-D immunoglobulin)

1. Anti-D immunoglobulin can prevent Rh-negative women from mounting an immune response (producing anti-D antibodies) when exposed to Rh-positive (D-positive) blood.
2. A dose of 300 µg of Rh immune globulin (RhoGAM) can protect (prevent immune response) from an exposure of up to 30 mL of fetal blood.
3. To prevent immunologic response, the patient must:
 - a. Not yet be sensitized to the D antigen
 - b. Be given enough immune globulin
 - c. Be treated in a timely fashion
4. Treatment of Rh-negative women within 72 hours of delivery decreases immunization to less than 1.5%.
5. Treatment of all Rh-negative women at 28 weeks' gestation further decreases risk of sensitization to less than 0.2%.
6. Other indications for use in pregnant Rh-negative, unsensitized women include:
 - a. Abortion (spontaneous or elective)
 - b. Ectopic pregnancy
 - c. Antepartum bleeding, including first and second trimester
 - d. Abdominal trauma

- e. After amniocentesis or chorionic villus sampling
- f. After external cephalic version
- 7. Failure to prevent sensitization may occur in the following conditions:
 - a. Inadequate dose (maternal exposure to more than 30 mL of fetal Rh-positive blood)
 - b. Treatment delay
 - c. Previously sensitized patient

E Management of the Rh-negative, unsensitized pregnant woman

1. Type and screen at initial visit.
2. If the patient is Rh negative, the father can be tested, and if he is also Rh negative, then there is no need to use RhoGAM.
3. Treat with Rh-immune globulin at 28 weeks (it is usual, although not necessary, to confirm that the patient is unsensitized prior to treatment).
4. Treat with Rh immune globulin after delivery (within 72 hours) if the fetus is Rh positive.
5. After delivery, check for “excessive” fetomaternal hemorrhage and treat with additional doses of Rh immune globulin if exposure is greater than 30 mL of fetal Rh-positive blood.
6. The amount of fetal–maternal hemorrhage can be estimated by the **Kleihauer–Betke** test. Treatment of maternal blood with acid elutes the adult hemoglobin from red cells, and only fetal hemoglobin remains. A smear is made and treated with a special stain that detects the red cells with fetal hemoglobin and the **volume of fetal red cells in the maternal circulation can be estimated.**

F Management of the Rh-negative, sensitized pregnant woman

1. Accurately assess gestational age with early ultrasound.
2. Determine **paternal blood type.**
 - a. If the partner is **Rh negative, there is no need for further evaluation and intervention.**
 - b. If the partner is homozygous for D, the fetus is D positive.
 - c. If the partner is heterozygous for D, the fetus has a 50% chance of being Rh negative and not at risk for anemia.
 - d. With amniocentesis or chorionic villus sampling, DNA analysis can be performed to evaluate whether the fetus is Rh positive.
 - e. Efforts are being made to assess fetal DNA sequences from maternal plasma with PCR
3. **Assess prior obstetric history.**
 - a. The risk of hemolytic disease tends to be as severe (or more severe) in subsequent pregnancies.
 - b. If the mother had a previous hydropic fetus, the risk that the next Rh-positive fetus will become hydropic is 80%.
 - c. Hemolysis and hydropic changes usually develop at earlier gestational ages with each successive pregnancy. In general, the risk of severe fetal hemolysis and hydropic changes in the first-sensitized pregnancy is low.
4. **Assess antibody titer.**
 - a. In the first-sensitized pregnancy, titers should be drawn every 2 to 4 weeks. Amniocentesis or noninvasive fetal evaluation should be offered when the “critical titer” is reached. In general, the critical titer is 1:16, and it signifies the titer at which a hydropic fetus has been identified. The critical titer is laboratory specific.
 - b. In subsequent-sensitized pregnancies, antibody titer is not as useful a guide to the timing of evaluation. The patient’s history should be used to guide the timing of evaluation and intervention.
5. **Use amniocentesis** to assess the degree of hemolysis and risk for fetal death. Once invasive testing is initiated, further assessment of antibody titers is not indicated.
 - a. **Bilirubin in amniotic fluid** is a by-product of fetal hemolysis.
 - b. Bilirubin enters the amniotic fluid from fetal secretions, and the level of bilirubin in amniotic fluid correlates with fetal hemolysis.
 - c. **Spectrophotometry** is used to assess the level of bilirubin in amniotic fluid.

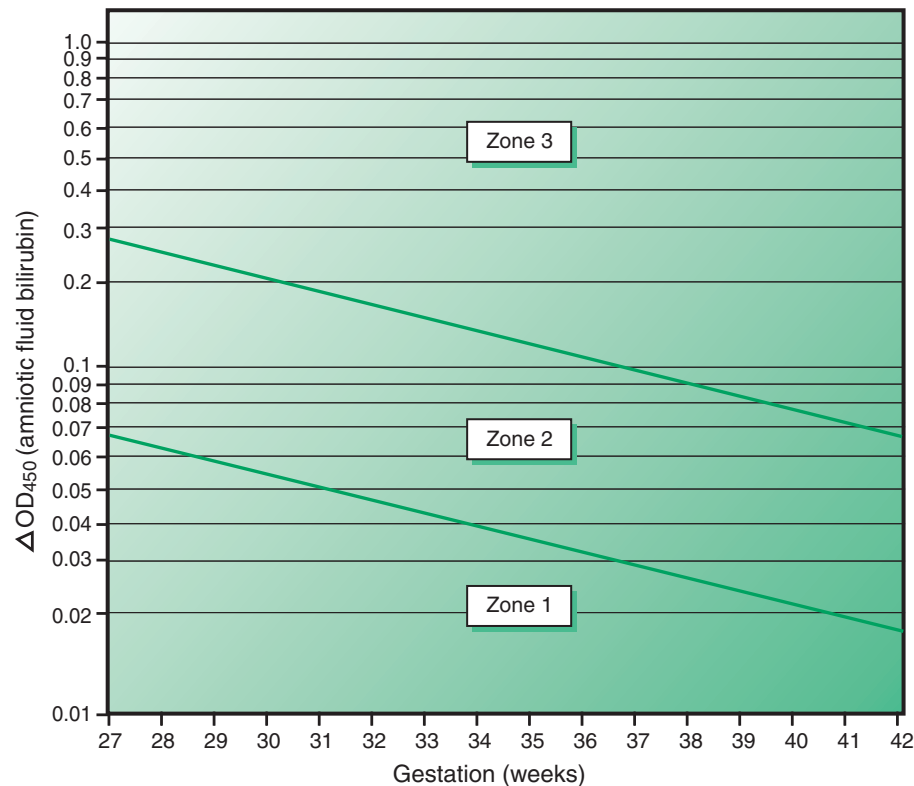


FIGURE 17-1 Liley curve. (From Pritchard JA, MacDonald PC, Gant NF. Williams Obstetrics. 21st Ed. New York: McGraw-Hill, 2001.)

- (1) Bilirubin causes a shift in optical density away from linearity.
- (2) Shift is greatest at a wavelength of 450 nm.
- (3) Degree of **shift at 450 nm (ΔOD_{450}) is used to estimate the degree of hemolysis.**
- d. In the early 1960s, Liley devised a chart on the basis of the natural history of Rh-sensitized pregnancies from **27 to 41 weeks' gestation**. The chart compares gestational age (x axis) versus assessment of ΔOD_{450} (y axis). Use of the **Liley curve** is associated with less iatrogenic premature delivery for those pregnancies at low risk of severe fetal anemia (Fig. 17-1).
 - (1) The chart is divided into three zones (marked by downsloping lines to reflect increased ability of the fetus to metabolize bilirubin with advancing gestational age).
 - (a) Zone I is associated with mild anemia or unaffected fetuses.
 - (b) Zone II is associated with mild to severe anemia.
 - (c) Zone III is associated with severe fetal anemia and fetal death within 7 to 10 days.
 - (2) Management of results in upper zone II or zone III includes cordocentesis to assess fetal hemoglobin, fetal transfusion, or delivery (depending on gestational age).
- e. Prior to 27 weeks, assessment of ΔOD_{450} values are based on a curve introduced by Queenan.
- f. **Amniocentesis** is associated with an **increased risk of sensitization, infection, rupture of membranes, and fetal loss.**
6. **Noninvasive assessment** of the fetus is now extremely useful in helping guide initial intervention. Techniques include ultrasound and Doppler velocimetry.
 - a. Ultrasound. Assessment of fetal anemia includes evidence of:
 - (1) Polyhydramnios
 - (2) Placental thickening
 - (3) Pleural effusions
 - (4) Pericardial effusions
 - (5) Ascites
 - (6) Increased liver size (suggestive of extramedullary hematopoiesis)

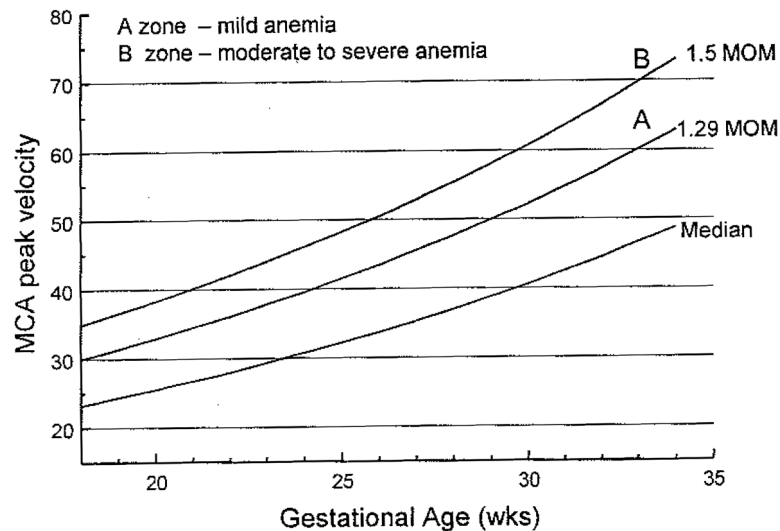


FIGURE 17-2 Middle cerebral artery (MCA) Doppler peak velocity based on gestational age. MoM, multiple of the median. (Moise KJ, Jr. Management of rhesus alloimmunization. *Obstet Gynecol* 2002;100:600–611.) Data from Mari G, for the Collaborative Group for Doppler Assessment of the Blood Velocity in Anemic Fetuses. Non invasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. *N Engl J Med* 2000;342:9–14.

- b. Doppler velocimetry. Not all severely anemic fetuses show evidence of hydropic changes. Doppler assessment is based on the premise that fetal anemia is associated with increased blood flow to preserve oxygenation. Fetuses with mild and moderate anemia usually have flow velocities in the normal range.
 - (1) Assess for increased peak velocity in the fetal middle cerebral artery (MCA). **Now considered the best tool for evaluating fetuses at risk** (Fig. 17–2). When MCA peak systolic velocity is elevated (above 1.5 MoMs), move to cordocentesis or delivery when near term.
 - (2) Assess for abnormal velocities in fetal aorta, inferior vena cava, or umbilical vein. These assessments not as sensitive or specific as use of MCA Doppler.
7. **Perform cordocentesis** when it is believed that the fetus is at risk for severe anemia.
 - a. This technique should be performed with a 22-gauge spinal needle under ultrasound guidance.
 - b. This technique may be performed along any portion of the umbilical cord, preferably in the umbilical vein (if transfusion is planned).
 - c. The initial sample should assess fetal hemoglobin and hematocrit, platelet count, reticulocyte count, and blood type.
 - d. Transfusion should occur if fetal hematocrit is less than 30%.
8. If necessary, **perform fetal transfusion either intraperitoneally or intravascularly** (through fetal umbilical vein). Intravascular transfusion instantly increases fetal hematocrit, whereas intraperitoneal transfusion requires the fetus to absorb transfused blood through the lymphatic system (severely anemic or hydropic fetuses may do very poorly). The goal is to raise fetal hematocrit.
 - a. Donor cells are matched with the mother and fetus (if available from prior cordocentesis).
 - b. Donor cells are buffy-coat poor, washed irradiated, filtered, and resuspended in normal saline to a hematocrit of 70% to 75%.
 - c. Nomograms exist to determine the amount to be transfused at one time based on donor and fetal hematocrit and on the gestational age of the fetus.
 - d. Once transfusion is complete, the final fetal hematocrit is assessed.
 - e. The procedure is repeated until the gestational age when the risks of prematurity are minimized. The timing of repeat procedures is based on fetal hematocrit and usually occurs within 2 to 3 weeks. At the time of the first repeat procedure, initial fetal hematocrit can help identify the rate of hemoglobin degradation to help determine the time of future procedures.
 - f. **Compared with amniocentesis, the risk of infection, rupture of membranes, fetal loss, and further sensitization are increased.**

- G Management of maternal sensitization for other antigens** In addition to the D antigen, red cells have hundreds of other antigens. The frequencies of these antigens depend on the population; fortunately, antibodies to many of these antigens do not place the fetus at risk for severe hemolytic disease. Other antigens that can pose a risk to the fetus by maternal antibody production include the other antigens in the Rh locus (c, C, e, and E), Kell, and Duffy. When a pregnant woman is sensitized to these antigens, the pregnancy is usually managed as outlined above for anti-D.



Study Questions for Chapter 17

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A 24-year-old primigravida is seeing you for her first prenatal visit. After confirming her pregnancy, you take a complete history and perform a physical examination. She has had type 2 diabetes for 6 years now and has been on oral medications for blood sugar control. Her capillary blood glucose level is 110 mg/dL today. After delivery, her newborn will be at risk for:

- ☐ A Elevated blood glucose
- ☐ B Low hematocrit
- ☐ C Low calcium
- ☐ D Elevated potassium
- ☐ E Low bilirubin

2. A 22-year-old woman, gravida 1, para 0, presents to you for prenatal care. Her history is notable for asthma since childhood. She has been followed by her primary and was on inhaled glucocorticoids which she stopped when she had a positive pregnancy test. Since then, she reports almost daily wheezing. What should be your first step in managing her asthma?

- ☐ A Start aminophylline
- ☐ B Educate her regarding use of beta-agonist inhalers
- ☐ C Restart her inhaled glucocorticoids
- ☐ D Prescribe a course of oral steroids
- ☐ E Start daily nebulized beta-agonists

3. A 28-year-old woman, gravida 2, para 1, at 20 weeks of gestation, presents with increased sweating and palpitations. Her fundus measures 17 cm. T = 98.8°F, BP = 115/80, P = 132, R = 16. She is found to have elevated total T₄, total T₃, and free T₄, and TSH less than 0.1. What is the initial step in management of this patient?

- ☐ A Propranolol
- ☐ B Methimazole
- ☐ C Propylthiouracil
- ☐ D Potassium iodide
- ☐ E Fetal ultrasound

4. An 18-year-old woman, gravida 3, para 2, at 28 weeks of gestation, is admitted with right-sided back pain, fever, chills, and severe nausea. She has bilateral costovertebral angle tenderness, with greater discomfort on the right side. T = 102.6°F, with normal complete blood count (CBC), blood urea nitrogen (BUN), and creatinine. Urinalysis revealed more than 100 WBC/hpf. After 3 days of culture-appropriate antibiotics, her temperature is still 103°F. The next step is:

- ☐ A Repeat urine culture
- ☐ B Repeat CBC
- ☐ C Change antibiotics
- ☐ D Perform an ultrasound
- ☐ E Perform an intravenous pyelogram (IVP)

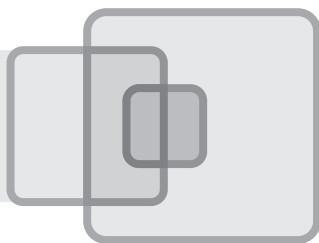
5. A 20-year-old woman just delivered a viable male neonate at 38 weeks of gestation after being a restrained passenger in a car accident. Upon arriving at the emergency department she was “cleared” by the trauma and orthopedic teams and sent to the labor and delivery floor. There she began having vaginal bleeding and then went into labor spontaneously. The estimated blood loss with delivery was 900 mL, and now she is stable. After obtaining her prenatal information you realize she is Rh negative and antibody D negative. The next step is:

- ☐ A Perform a CBC
- ☐ B Transfuse packed red blood cells
- ☐ C Perform a Kleihauer–Betke test
- ☐ D Give additional Rh immune globulin
- ☐ E Assess neonatal Rh antigen status



Answers and Explanations

1. **The answer is C** [I B 2]. A diabetic woman is at higher risk for delivering a baby with respiratory distress, hypoglycemia (low glucose), hypocalcemia (low calcium), polycythemia (high hematocrit), and hyperbilirubinemia (high bilirubin). Potassium levels are usually not affected.
2. **The answer is C** [IV C 3 b]. For women with persistent asthma, inhaled glucocorticoid is first-line therapy. The goal of therapy is to prevent maternal hypoxic episodes. Short acting inhaled beta-agonists are used for rescue therapy, while use of nebulizers and IV steroids are used for acute, severe exacerbations. After IV steroids, a course of oral steroids is used as a taper. Those with severe asthma may require courses of oral steroids for control when inhaled glucocorticoids and beta-agonists are not sufficient. Education regarding use of inhalers is important, as is immediate follow-up with a change in a patient's symptoms.
3. **The answer is A** [II B 4 a 3]. This patient has hyperthyroidism based on her elevated free T_4 levels and suppressed TSH. Beta-blockers are the initial treatment of choice for her symptoms of tachycardia and palpitations. For this patient, PTU is also necessary to maintain her free T_4 levels near high normal. However, PTU is not the initial treatment to control her significant tachycardia. Methimazole is not used often because it is associated with aplasia cutis and the alternative agent, PTU, is safer. Potassium iodide is one of the agents used to treat a thyroid storm. A fetal ultrasound would be appropriate given the disparity between the gestational age and the fundal height. However, an ultrasound is not the initial step, nor is it a step that will solve this patient's problems.
4. **The answer is D** [III D 5 d]. The clinical scenario presented is that of pyelonephritis that is not responding to treatment. This finding should always prompt radiologic evaluation to rule out an abscess or renal calculi. The least invasive initial procedure is a renal ultrasound, not an intravenous pyelogram. There is no need to repeat the urine culture or to change her antibiotics since results of her initial urine culture and sensitivity confirm that she is on appropriate antibiotics. Repeating CBC is fine, but it will not tell you why there is lack of response to treatment.
5. **The answer is E** [IX E 3]. In the management of an Rh-negative, unsensitized (i.e., antibody-negative) patient, you should know the Rh antigen status of the baby. If the baby is Rh negative, then there is no need for Rh immune globulin because the maternal immune system would not form any antibodies directed toward fetal red blood cells. Had the baby been Rh positive, the next step would be to quantitate the amount of fetomaternal blood transfusion by performing a Kleihauer–Betke test. Then, based on those results, you may give additional Rh immune globulin. A CBC or transfusion is not necessary in this scenario because this patient stopped bleeding and is “stable.” A CBC or capillary hemoglobin concentration test is appropriate during the first postpartum day for all postpartum patients.



The Gynecologic Office Visit

PETER J. VASQUEZ • JENELL S. COLEMAN

I

INTRODUCTION

The gynecologist is in the unique position of providing both primary and specialty care for women. Many women see their gynecologist for routine health maintenance, in addition to preventive care and treatment for gynecologic conditions. The gynecologic office visit differs for adolescents, premenopausal, and postmenopausal women, but at all ages serves to address the unique aspects of reproductive health as well as primary and preventative care. This chapter will focus on the reproductive health aspects of office gynecology.

II

OFFICE GYNECOLOGY IN THE ADOLESCENT

Adolescence is a period of major changes in a girl's life beginning from approximately age 10 until age 21. She undergoes physical, emotional, and cognitive changes. The practitioner must be particularly sensitive to the unique needs and communicative style of an adolescent female. She may welcome the continued presence and comfort of her guardian during the history and physical examination. As she feels more comfortable with accessing healthcare and matures, she will eventually visit with the provider alone. However, this is typically during the late teen years or once sexual activity has been initiated (see Chapter 20).

A History

1. General
 - a. Engage both the patient and the accompanying guardian.
 - b. Allow the adolescent to speak and describe the condition to the best of her ability and then complete the history through involvement of the parent.
2. Social history
 - a. Begin the visit by asking questions regarding neutral topics to establish rapport.
 - b. Performance in school: affords a picture of the home environment, intellect, and general well-being.
3. Medical history
 - a. Chronic medical conditions
 - b. Prescribed medications
4. Menstrual history: The purpose of the menstrual history is to establish the patient's menstrual bleeding pattern to determine whether there are any abnormalities that may signal an underlying pathologic condition. This history includes:
 - a. Age at menarche. The mean age of menarche in the United States is between 12 and 13 years old.
 - b. Interval between periods. The average interval between menses is 28 days. A normal interval is considered to be between 21 and 35 days.
 - c. Duration of menses. Normal menses last between 2 and 6 days.
 - d. Characteristics of flow. The average blood loss during each menses is between 20 and 60 mL.
 - e. Regularity. Regular menses are a reliable sign of ovulation, and conversely, oligomenorrhea often signals anovulation. Menses may be irregular for the first 2 years following menarche due to maturation of hypothalamic–pituitary–ovarian axis.

- f. Dysmenorrhea. It refers to pain during menses. It is described as primary dysmenorrhea when no cause can be found. Secondary dysmenorrhea refers to menstrual pain attributable to other factors that in an adolescent could be due to endometriosis or pelvic inflammatory disease.
 - g. Associated symptoms (e.g., breast tenderness, bloating, and mood change).
 - h. Recent changes in the menstrual pattern.
5. Other: In certain circumstances, the guardian should be asked to leave the room in order to allow a more intimate discussion.
- a. Sexuality: ranges from having a crush to sexual exploration (i.e., heavy petting and kissing) to sexual intercourse (i.e., oral, anal, and vaginal intercourse).
 - b. Information should be obtained regarding the sex of the partner, age, relationship, and whether it was consensual.
 - (1) Depending on the ages specified by State Law, this behavior may have to be legally reported and the patient and parents should be made aware.
 - c. Safety and abuse: Does she feel safe at home? At school? Does she get into fights with her friends or boyfriend? Adolescents may not view fighting with a boyfriend as abuse but direct questioning may elicit this information.
 - d. Risky behaviors: use of tobacco, drugs, and alcohol. Ask about risky behavior of her peer group. Adolescents are under tremendous “peer pressure” and the provider has the opportunity to reinforce positive behaviors through encouragement.

B Physical examination

1. Height and weight: important measures to assess health and if forming a differential diagnosis for a specific problem. Inadequate or excess weight may directly affect the menstrual cycle.
2. Tanner staging (see Chapter 20).
 - a. Breasts: assess developmental stage and evaluate for common findings include asymmetry or benign rubbery tumors called fibroadenomas.
 - b. Pubic hair assess developmental stage.
3. Pelvic examination is not indicated unless the patient is having a specific problem or is sexually active or at the age when Pap smear screening is indicated. Many adolescents are anxious about visiting the gynecologist. To place the patient at ease, use of pictures, diagrams, and a basic description of the examination are helpful. When an examination is indicated:
 - a. Positioning: frog-leg, knee-chest, or lithotomy offer visualization of the external genitalia.
 - b. Common complaints may be investigated by use of imaging such as ultrasound or MRI.

C Specimen sampling

1. Urine sample: it is useful in cases of urinary tract infections, testing for sexually transmitted infections (STIs) such as gonorrhea and chlamydia, and testing for pregnancy.
2. Vaginal microscopy: a moistened, cotton-tipped applicator can be blindly inserted into the vagina by either the patient or the provider in order to examine vaginal discharge using microscopy.
 - a. Conditions such as yeast vaginitis, trichomoniasis, atrophic vaginitis, bacterial vaginosis, and cervicitis can be ascertained.
3. Microbiology: applicator swabs may also be blindly inserted to determine the vaginal flora.
4. Pap smear screening for cervical cytology is not indicated until age 21.

- D Preventative** It is the pediatrician who will routinely interview and examine the patient to provide basic and preventative care, that is, human papilloma virus (HPV) vaccination and school physicals. The role of the gynecologist is to provide specialty care.

III

OFFICE GYNECOLOGY IN THE WOMEN OF REPRODUCTIVE AGE

Women of reproductive age are generally advised to have a gynecologic examination annually. This examination includes a complete general history and physical examination, as well as a more focused gynecologic history and physical examination. The information gained may be used to diagnose and manage a variety of conditions that are described elsewhere in this book.

A Gynecologic history

1. Menstrual history.
2. Sexual history. A sexual history is an important part of the gynecologic history, as other providers may not elicit this from the patient. An open and nonjudgmental approach to the sexual history will facilitate gathering this important information, which can be used to counsel the patient about pregnancy planning, prevention of STI, and sexual health.
 - a. Age at first coitus.
 - b. Sex of partners. Inquire if the patient's sexual partners are male, female, or both.
 - c. Current sexual activity, forms of sex she engages in and number of partners.
 - d. Sexual difficulties. Sexual dysfunction is a relatively common problem that patients may be reluctant to bring up.
 - (1) Dyspareunia, or painful intercourse, may be due to a variety of causes including vaginal dryness, endometriosis, fibroids, or anxiety.
 - (2) Decreased sexual interest and response are also common problems that may be related to physiologic or psychologic causes.
 - e. History of sexual abuse or assault and nonconsensual sex are common occurrences. It is important to remember that women may not classify sexual abuse that occurs within a relationship as abuse.
3. Obstetric history. A detailed obstetric history allows the provider to counsel about future pregnancy and delivery, and to identify risk factors for pregnancy complications.
 - a. Gravidity and parity: number of times she has been pregnant, and the results of each of those pregnancies
 - b. Complications of pregnancy and delivery in order to anticipate possible complications of future pregnancies
 - c. Mode of delivery. A patient's future delivery plans may depend on her prior deliveries
4. Contraception. Many women see their gynecologist for contraceptive management. The gynecologic provider should address this issue at each visit to ensure the patient's contraceptive goals are being met.
 - a. All women of childbearing age should be asked about long- and short-term plans for childbearing and contraception.
 - b. Inquire about the patient's current method of contraception and whether it is acceptable to her and offer alternate means of contraception if indicated.
 - c. Ask about past methods of contraception and why the patient discontinued them can provide useful information for contraceptive counseling.
5. Cervical cytology history. The patient's cervical cytology history should be elicited to ensure that she is getting the appropriate follow-up for any abnormal cytology. This is also a good opportunity to educate the patient about the purpose and importance of regular cervical dysplasia screening and protection against STIs.
 - a. Last Pap test. See below for current recommendations on frequency of cervical cytology.
 - b. History of any abnormal Pap tests: when it occurred and what the abnormality was.
 - c. Any history of a colposcopy to assess history of dysplasia.
 - d. History of excisional procedures. Patients with persistent and/or preinvasive lesions may undergo an excisional procedure such as a cold-knife cone biopsy (CKC) or loop electrode excisional procedure (LEEP).
6. Pelvic infections. Both sexually and non-STIs are relatively common, and both types may be asymptomatic. Any woman with a complaint of new or different vaginal discharge, irritation, itching, or lesion should be evaluated for pelvic infections.
 - a. STIs have important consequences, both in terms of the individual's health and public health.
 - b. History of gonorrhea, chlamydia, herpes, trichomonas, HIV, or any other STI. Severity of infection to assess risk for ectopic pregnancy or infertility. The adequacy of treatment should be determined, as well as if the woman's sexual partners have been treated.
 - c. History of non-STIs such as bacterial vaginosis or candida.
7. Gynecologic procedures. The history of gynecologic procedures and surgeries may be elicited as part of the general surgical history, or within the gynecologic history.

- a. Office procedures: such as an endometrial biopsy, vulvar biopsy, or drainage of a Bartholin's gland cyst.
 - b. Operative gynecologic procedures hysteroscopy, dilation and curettage, tubal ligation, myomectomy, hysterectomy, and salpingo-oophorectomy.
8. Other gynecologic conditions or diagnoses. The patient may present to a gynecologist already carrying a diagnosis of a condition specific to the reproductive tract. These specific conditions should be assessed and investigated when appropriate.
- a. Endometriosis
 - b. Fibroids
 - c. Infertility
 - d. Incontinence
 - e. Prolapse
 - f. Breast conditions

B Gynecologic physical examination A focused gynecologic examination is often performed as part of a general physical examination during a routine gynecologic visit. Because this examination is often uncomfortable for the patient, it is important to pay attention to patient positioning and draping. Both male and female providers are encouraged to have a nurse or medical assistant present to assist and chaperone the examination.

1. External. The examination begins with inspection of the external genitalia. The pubic hair pattern provides information about pubertal development and evidence of androgen excess with male pattern distribution of pubic hair. The labia majora are inspected for any swelling or lesions, and the Bartholin glands may be gently palpated. The labial majora are then separated to reveal the labia minora, clitoris, urethral meatus, and vaginal introitus. The examiner should note any abnormalities such as clitoromegaly, imperforate hymen, prolapse, or female genital cutting ("female circumcision").
2. Speculum examination. A speculum examination is performed to visualize the vagina and cervix. Specula are made in a variety of shapes and sizes, and the smallest one that allows adequate visualization should be chosen. The speculum may be lubricated with water or surgical lubricant prior to insertion. When the speculum has been properly inserted the cervix is fully visualized. The examiner should note the size and shape of the cervix, and any visible abnormalities. The presence and characteristics of any vaginal discharge should be noted. A Pap test, cultures for gonorrhea and chlamydia, and a sampling of vaginal discharge for office microscopy can be performed at this time. As the speculum is withdrawn, the vaginal walls should be inspected for any lesions.
3. Bimanual examination. The bimanual examination allows the provider to assess the cervix, uterus, and adnexa. Two fingers are inserted into the vagina and used to elevate the uterus. The cervical os can be inspected and its dilation noted. An antverted uterus can be felt by pressing with the other hand against the lower abdominal wall. A retroverted uterus often cannot be felt. Deep palpation lateral to the uterus may reveal the adnexa. The examiner should note any abnormalities, such as an enlarged or irregular uterus, adnexal tenderness, or an adnexal mass.
4. Breast examination. An annual clinical breast examination is a useful adjunct to mammography in the detection of breast cancer, as well as benign breast lesions. Prior to the examination, the patient should be asked if she has noted any changes in her breasts, such as new lumps or masses, changes in size or shape, skin changes, or nipple discharge. The examination begins with the patient sitting with hands on her hips. The breasts are visually inspected then systematically palpated for masses, and lymphadenopathy. The position of any abnormality is described in terms of clock position and distance from the nipple. Lumps or masses should be classified as to size, texture, irregularity, and mobility.

C Diagnostic and screening procedures Routine health maintenance in the form of screening tests is an integral part of the gynecologic office visit.

1. Pap test: Many women equate a gynecologic office visit with a Pap test, and this is in fact an important component of the visit. Guidelines for cervical cytology have recently changed.

- a. The current recommendation is to begin screening at age 21.
 - b. Cytologic testing should be performed every 2 years from ages 21 to 29.
 - c. Women above 30 years old may have testing spaced to every 3 years if they have had three consecutive normal Pap tests, and no history of cervical dysplasia or compromised immune function.
 - d. The optimal age to stop screening is unknown, but most expert opinion recommends discontinuing routine cervical cytology at 65 or 70 years of age, taking into account the patient's past history of cervical abnormalities and current sexual practices.
 - e. HPV testing. HPV infection is implicated in almost all cases of cervical cancer. High sensitivity tests exist to determine the presence of oncogenic forms of HPV. This testing can be done at the same time as liquid-based cervical cytology.
 - f. Interpretation. The results of cervical cytology are generally reported according to the Bethesda system, last updated in 2001.
 - (1) Adequacy
 - (2) Negative for intraepithelial lesions
 - (3) Atypical squamous cells (ASC)
 - (4) Atypical glandular cells (AGC)
 - (5) Low-grade squamous intraepithelial lesions (LSIL)
 - (6) High-grade squamous intraepithelial lesions (HSIL)
 - (7) Squamous cell carcinoma
 - g. Follow-up. The American Society for Colposcopy and Cervical Pathology publishes comprehensive algorithms for the management of cervical cytological abnormalities.
2. STI screening: Recommendations for routine screening for STIs are based on the specific infection, the patient's age, and her risk factors.
 - a. *Chlamydia trachomatis* and *Neisseria gonorrhoeae*
 - (1) All women 25 years old and younger should be screened for chlamydia and gonorrhea. These infections are both common and often asymptomatic.
 - (2) Women of any age may be screened if they have risk factors such as a partner with a known infection, unprotected sex with multiple partners, or other STIs.
 - (3) Testing can be performed on a urine sample, a cervical or vaginal swab, or on a liquid-based cervical cytology sample.
 - b. Trichomoniasis
 - (1) STI caused by a flagellated organism *Trichomonas vaginalis*.
 - (2) Yellow malodorous vaginal discharge and irritation, but may be asymptomatic.
 - (3) Wet mount will reveal small motile organisms and KOH preparation will reveal a fishy odor (amine whiff test).
 - c. HIV. Women should be offered screening on the basis of the risk factors such as sex work, unprotected sex with multiple partners, partner with known infection, intravenous drug abuse, or other STI.
 - d. Hepatitis C. The guidelines for screening are the same as for HIV. Because of its high transmissibility as a blood-borne pathogen, women who have received multiple blood transfusions prior to 1990 should be screened.
 - e. Syphilis. Patients should be offered screening if they have any clinical signs of symptoms of syphilis infection, or risk factors such as unprotected sex with multiple partners or a partner with a known infection.
 - f. Herpes simplex virus. Current guidelines do not recommend testing for herpes in average risk, asymptomatic patients. However, high-risk asymptomatic women may undergo serologic testing using type-specific antibody tests as lesions may occur within the lower genital tract.
 3. Mammography. Currently, guidelines for mammography are undergoing change.
 - a. The United States Preventative Services Task Force recently issued new guidelines suggesting targeted screening on the basis of the risk factors for women aged 40 to 49, and universal screening every 2 years beginning at age 50.
 - b. The American College of Obstetricians and Gynecologists, however, continues to follow previous guidelines, and recommends universal screening mammography annually beginning at age 40.

IV

OFFICE GYNECOLOGY IN THE POSTMENOPAUSAL WOMEN

Menopausal women continue to have many of the same healthcare needs as women of reproductive age, and are advised to continue annual gynecologic examinations. However, there are a number of unique needs in this age group.

A Menopause

1. Average age of menopause, defined as the absence of menses for 12 months, is 51. Menopause is preceded by a perimenopausal period of varying duration. During this time, the patient experiences menstrual irregularity and the beginning of vasomotor symptoms such as hot flashes and night sweats.
2. Physiologic changes. The fundamental physiologic change in menopause is a decrease in estradiol due to depletion of oocytes and is associated with oligo- or anovulation.
3. Clinical
 - a. Vasomotor symptoms, commonly experienced as hot flashes and night sweats experienced by up to 75% of menopausal women. The exact pathophysiologic mechanism remains unknown. Estrogen deficiency undoubtedly plays a role, as evidenced by the improvement in symptoms with hormone replacement therapy.
 - b. Vulvar and vaginal atrophy leading to vaginal dryness and irritation especially with sexual activity.
 - c. Resolution of symptoms from symptomatic fibroids, endometriosis, and adenomyosis in the postmenopausal period.
 - d. Decrease in pelvic musculature support, resulting in pelvic organ prolapse.
4. Postmenopausal bleeding. Following menopause uterine bleeding is always abnormal and must be evaluated.
 - a. Vaginal atrophy is a common benign cause of postmenopausal bleeding.
 - b. Endometrial hyperplasia and endometrial cancer. Therefore, endometrial biopsy is generally recommended to evaluate postmenopausal bleeding.

B Sexuality

1. Dyspareunia due to atrophic vaginitis leading to decreased lubrication and subsequent irritation during sexual activity.
2. Decrease in libido.
3. STI prevention. Although barrier methods are no longer needed for contraception, women should be reminded to protect themselves from STIs.

C Bone health The hypoestrogenic state associated with menopause leads to a decrease in bone mineral density. Bone resorption increases in the absence of estrogen, while bone formation remains the same. Menopausal women therefore have an increased risk of osteopenia and osteoporosis, which are risk factors for bone fractures.

1. Adequate dietary calcium and vitamin D. Recommended daily allowance (RDA) are:
 - a. Calcium intake 1,200 mg daily
 - b. Vitamin D3 1,000 IU daily
2. Weight-bearing exercise has been demonstrated to decrease fracture risk.
3. Screening. The best screening modality for bone density is the dual energy X-ray absorptiometry (DEXA) scan. Current guidelines recommend universal screening with DEXA beginning at age 65, or age 50 in women with risk factors.

V

OFFICE GYNECOLOGY IN WOMEN IN SAME-SEX RELATIONSHIPS

In general, lesbian and bisexual women have the same healthcare needs as heterosexual women. However, they may be less likely to access care for fear of judgments or assumptions about their sexual orientations. Additionally, healthcare providers may be reluctant to discuss their patients' sexual orientation due to lack of knowledge or comfort. This section will focus on aspects of the gynecologic examination that may be unique to women in same-sex relationships.

- A STI screening** Women who have sex with women (WSW) have somewhat different risk factors for STI acquisition.
1. STIs which are known to be transmissible between women include HSV, HPV, and trichomoniasis.
 2. STIs with a theoretical risk of transmission include gonorrhea, chlamydia, syphilis, hepatitis B and C, and HIV.
 3. WSW may have or have had male partners who have put them at risk for STIs including HPV.
- B Cervical cytology** HPV-associated lesions have been found in women who have never had a male partner. Therefore, cervical cytology screening recommendations are the same for lesbian and bisexual women.
- C Fertility** Women in same-sex relationships should be asked about their desire for childbearing and contraception. Patients who desire children may need the assistance of a specialist in assisted reproductive technologies.
- D Domestic violence** Women in same-sex relationships are not immune from intimate partner violence. However, they may be even less likely to report abuse than women in heterosexual relationships. Providers should screen WSW for domestic violence as they do for all patients.



Study Questions for Chapter 18

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A healthy 12-year-old girl complains of several weeks of vaginal itching. She denies having vaginal discharge or a foul odor. The patient leads an active lifestyle—she is on the swim team, plays soccer, and performs gymnastics. She does well in school and desires to become a veterinarian. Her mother accompanies her to the office visit. You suspect a vaginal yeast infection and would like to prepare a slide for microscopy. The appropriate steps include:

- ☐ A Request the mother to leave the room while you place the patient in stirrups. You then perform a speculum examination to obtain vaginal discharge with the assistance of an aide
- ☐ B Ask the mother to stay present and to assist you with the examination. You then place the patient in the frog-leg position, request a moistened cotton-tipped swab from the medical assistant. You ask the patient to gently insert the swab into the vagina and swirl
- ☐ C Hand the patient a moistened cotton-tipped swab. You then ask her to go into the restroom, insert the swab into the vagina, and return the swab to you
- ☐ D Ask the patient if she would like her mother to stay. You then place the patient in the lithotomy position using stirrups and request a moistened cotton-tipped swab from the medical assistant. You gently insert the swab into the vagina to collect discharge
- ☐ E Both B and D are correct

2. A 24-year-old G1P1001 woman presents for a routine examination. She has no specific gynecologic complaints. She is in a monogamous relationship with her husband of 3 years. Her last gynecologic visit was 1 year ago, at which time she had a normal Pap smear. The appropriate screening for STIs includes:

- ☐ A None. She is in a monogamous relationship
- ☐ B Gonorrhea, chlamydia, HIV, hepatitis C, syphilis, herpes, and trichomonas
- ☐ C Gonorrhea and chlamydia only
- ☐ D Gonorrhea, chlamydia, and HIV
- ☐ E HIV and hepatitis C, as she is asymptomatic for other infections

3. A 33-year-old G3P2012 presents for an annual examination. She had a Pap smear showing ASC-US at age 22. She has received annual Pap tests since that time and all have been normal. She is in a monogamous relationship with her husband of 15 years. She had never had an STI. She uses an IUD for birth control. She asks you how she should be screened for cervical cancer. You inform her:

- ☐ A She should continue annual Pap tests without HPV testing
- ☐ B She may undergo Pap tests every 3 years
- ☐ C If she has a negative Pap test and negative HPV test this year, she does not need further evaluation for at least 3 years
- ☐ D She does not need any further cervical cytology screening
- ☐ E Both B and C are correct

4. A 62-year-old G2P2002 presents for a routine examination. Her last period was 10 years ago and she has had no postmenopausal bleeding. She brings a copy of her records that indicate a history of normal Pap tests for the past 20 years, with the most recent 1 year ago. Her last mammogram was 2 years ago. She takes a calcium and vitamin D supplement. She took estrogen and progesterone replacement therapy in early menopause but stopped 8 years ago. Her vasomotor symptoms are minimal. She is otherwise healthy and on no medications. She has no family history of breast or ovarian cancer. You recommend the following screening tests.

- ☐ A Pap test
- ☐ B Mammogram
- ☐ C DEXA scan
- ☐ D All of the above
- ☐ E None of the above

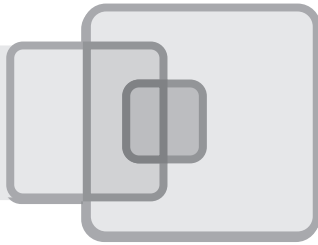
5. A 29-year-old nulligravida comes to your office due to vaginal discharge for 3 weeks. The discharge is described as yellow-green, copious, and malodorous. She also has vulvar irritation. She informs you that she has been in a monogamous same-sex relationship for 3 years. She otherwise has no complaints. The most appropriate next step in management is to:

- ☐ A Inform the patient that because she is a lesbian she is essentially at no risk for STIs, and screening is not indicated
- ☐ B Empirically treat her for gonorrhea and chlamydia with azithromycin and ceftriaxone
- ☐ C Encourage vulvar hygiene and abstinence from sexual activity until the symptoms resolve
- ☐ D Order comprehensive STI screening for gonorrhea, chlamydia, herpes, HIV, hepatitis, and trichomoniasis
- ☐ E Obtain a vaginal swab for office microscopy to assess for bacterial vaginosis and trichomoniasis



Answers and Explanations

1. **The answer is E.** Adolescents mature at different rates. You will be able to determine if she appears to be more mature than her peers or independent and would like to be examined alone. If the patient appears frightened, then it is wise to ask the parent to stay in the room during the examination for patient's comfort. A blind-swab may be inserted by the patient under your guidance. Answer C is incorrect because it does not allow for external visualization of the vulva and proper collection technique cannot be assured. Answer A is incorrect because a speculum examination is not indicated in this example.
2. **The answer is C.** Current guidelines recommend routine testing only for gonorrhea and chlamydia in patients 25 years of age and younger. Although the patient is in a monogamous relationship, she should still be tested for these relatively common and often asymptomatic infections. More comprehensive testing, including syphilis, HIV, hepatitis, and trichomoniasis is recommended for the symptomatic patient, or for patients with risk factors for acquiring these diseases.
3. **The answer is E.** In this low-risk patient with a history of negative cervical cytology for the past 3 consecutive years, two screening strategies are appropriate. She may either undergo cervical cytology alone, or cervical cytology and HPV testing. The latter has increased sensitivity when compared to cytology alone, and may allow the screening interval to be extended beyond 3 years. Current recommendations do not support annual testing in this patient. However, it is inappropriate to discontinue screening altogether.
4. **The answer is B.** This patient should be ordered for a mammogram. Regardless of which guidelines are used, this patient should receive a mammogram, as she is older than 50 years and last had a mammogram 2 years ago. Given her history of normal Pap tests, and recent Pap test 1 year ago, she does not need another Pap test for 2 years. She is younger than 65 years, and has no identifiable risk factors for osteoporosis, and therefore does not need a DEXA scan until age 65.
5. **The answer is E.** The patient's clinical presentation is suspicious for trichomoniasis or bacterial vaginosis. Trichomoniasis is known to be a disease that can be transmitted sexually in women who have sex with women. The next appropriate step in management is to attempt to identify the causative organism on office microscopy. It is inappropriate to assume that the patient's sexual orientation precludes her from acquiring an STI. Conservative treatment with observation is also not an appropriate strategy in this symptomatic patient. Gonorrhea or chlamydia is a less likely possibility than trichomoniasis or bacterial vaginosis, so empiric treatment is inappropriate. Comprehensive STI screening is not indicated. However, if office microscopy is negative for trichomoniasis or bacterial vaginosis, focused STI screening for gonorrhea and chlamydia may be appropriate.



The Menstrual Cycle

MARY E. RAUSCH • CLARISA GRACIA

I

INTRODUCTION

The menstrual cycle relies on the cyclic production of estrogen and progesterone that mirrors the regular occurrence of ovulation throughout a woman's reproductive life. The development of predictable, regular cyclic, and spontaneous ovulatory menstrual cycles is regulated by complex interactions of the hypothalamic–pituitary axis, the ovaries, and the genital tract. The menstrual cycle is divided into two phases: the follicular (or proliferative) phase and the luteal (or secretory) phase.

A Length of the cycle

1. The **mean duration** of the cycle is **28 days**, plus or minus 7 days.
 - a. **Polymenorrhea** is defined as menstrual cycles that occur at short intervals (less than 21 days).
 - b. **Oligomenorrhea** is defined as menstrual cycles that occur at long intervals (more than 35 days).
2. Menstrual cycles are the most irregular during the 2 years following menarche (i.e., the first menses) and during the 3 years leading up to menopause. At both times, **anovulation** (i.e., absent ovulation) is most common.

B Follicular or proliferative phase This phase lasts from the first day of menses until the luteinizing hormone (LH) surge, during which time follicles within the ovary grow in response to **follicle-stimulating hormone (FSH)**, and in the uterus **endometrial glands** proliferate under the influence of **estrogen**, primarily **estradiol** produced by the follicle. The follicular phase is characterized by:

1. Variable length, although it averages 14 days, which is responsible for the variation in cycle length between women and for a particular woman
2. Development of ovarian follicles in response to FSH (the “follicular” phase)
3. Secretion of estrogen (primarily estradiol) from the ovary
4. Proliferation of the endometrium in response to estrogen (the “proliferative” phase)
5. Low basal body temperature

C Ovulation Ovulation occurs in response to the **LH** surge. This phase is characterized by:

1. Release of the oocyte from the follicle in response to FSH induction of collagenases, which enzymatically break down the follicle wall
2. Resumption of meiosis, with oocytes progressing from prophase I through metaphase II
3. Formation of the corpus luteum within the follicle

D Luteal or secretory phase The second part of the cycle extends from ovulation until the onset of menses. The corpus luteum, stimulated by LH, produces progesterone, which causes secretory changes in the endometrium necessary for preparing the endometrium for implantation of the embryo. The luteal phase is characterized by:

1. A fairly constant duration of 14 days, plus or minus 2 days, in contrast to the follicular phase
2. An elevated basal body temperature (higher than 98°F) in response to progesterone production
3. Sustaining of the **corpus luteum** in the ovary, with the secretion of progesterone and estrogen (the “luteal” phase)

4. Secretory changes in the endometrium including gland tortuosity and secretion, stromal edema, and a decidual reaction (the “secretory” phase)

E Neuroendocrine control by the hypothalamic–pituitary–gonadal axis The integration of the menstrual cycle involves the interaction among **gonadotropin-releasing hormone** (GnRH) produced in the hypothalamus, the pituitary **gonadotropins** (FSH and LH), and the ovarian **sex steroids** (i.e., androstenedione, testosterone, estradiol, estrone, and progesterone).

II

GONADOTROPIN-RELEASING HORMONE

GnRH is the hypothalamic hormone that controls gonadotropin release.

A Characteristics

1. This hormone, a decapeptide, is produced by hypothalamic neurons, principally from the arcuate nucleus, and is transported along axons that terminate in the median eminence around capillaries of the primary portal plexus.
2. It is secreted into the portal circulation, which carries it to the anterior lobe of the pituitary gland.

B Secretion

1. GnRH is secreted in a **pulsatile manner**; the amplitude and frequency of the secretions vary throughout the cycle, with a lower pulse amplitude and higher frequency in the follicular phase.
 - a. One pulse every 60 to 90 minutes is typical of the follicular phase.
 - b. The pulse frequency slows to every 2 to 3 hours in the luteal phase.
2. The **amplitude and frequency** are regulated by:
 - a. Feedback of estrogen and progesterone
 - b. Neurotransmitters within the brain, mainly the catecholamines dopamine (inhibitory) and norepinephrine (facilitatory)

C Action of GnRH on gonadotropin production

1. When GnRH binds to specific receptors on the surface membrane of target cells, it acts through secondary messengers to activate protein kinase and changes the concentration of **cyclic adenosine monophosphate (cAMP)**.
2. This stimulates the synthesis and storage of both FSH and LH from the same cell.
3. GnRH activates and moves gonadotropins from the reserve pool to a pool ready for secretion, which leads to their immediate release.
4. High, continuous, or prolonged GnRH exposure in the pituitary saturates the GnRH receptors and inhibits FSH and LH secretion. This is called desensitization or **downregulation**.

III

GONADOTROPINS: FOLLICLE-STIMULATING HORMONE AND LUTEINIZING HORMONE

A FSH is responsible for production of estrogen and growth of the follicle. **FSH receptors** exist primarily on the ovarian **granulosa cell membrane**. FSH stimulates follicular growth by:

1. Increasing the number of FSH and LH receptors on granulosa cells.
2. Increasing the number of granulosa cells by stimulating granulosa cell mitosis in the presence of estrogen.
3. Stimulating conversion of androgens to estrogens within the granulosa cell by the enzyme aromatase.

B LH is responsible for the initiation of the luteal phase (ovulation) and maintenance of the luteal phase of the menstrual cycle. **LH receptors** exist on ovarian **theca cells** at all stages of the cycle and on **granulosa cells** after the follicle matures under the influence of FSH and estradiol.

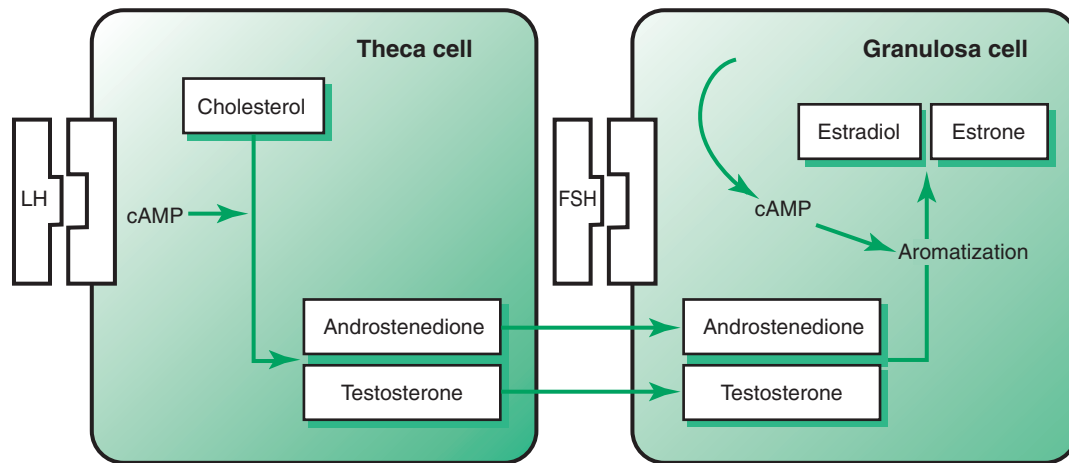


FIGURE 19–1 Two-cell hypothesis of estrogen production. cAMP, cyclic adenosine monophosphate; FSH, follicle-stimulating hormone; LH, luteinizing hormone. (Reprinted with permission from Speroff L, Glass RH, Kase NG. Regulation of the menstrual cycle. In: Speroff L, Glass RH, Kase NG, eds. *Clinical Gynecologic Endocrinology and Infertility*. 4th Ed. Baltimore: Williams & Wilkins, 1999:207).

1. LH stimulates **androgen synthesis** by the theca cells.
2. With a sufficient number of LH receptors on the granulosa cells, LH acts directly on the granulosa cells to cause ovulation.
3. Following ovulation, LH stimulates production of progesterone from the luteinized granulosa cells in the corpus luteum.

C Two-cell hypothesis of estrogen production (Fig. 19–1)

1. LH acts on the theca cells to stimulate the conversion of cholesterol to androgens (i.e., androstenedione and testosterone).
2. Androgens are transported from the theca cells to the granulosa cells.
3. Under the influence of FSH, androgens are aromatized to form estrogens (i.e., estradiol and estrone) by the enzyme aromatase in the granulosa cells.

IV

OÖGENESIS

A Oocyte formation and decline

1. During embryogenesis, germ cells begin to multiply rapidly by mitosis and peak at 6 to 7 million oogonia in the 20th week of gestation.
2. Oogonia become primary oocytes when they enter meiosis and are arrested in prophase of the first meiotic division.
3. Oocytes are rapidly lost before birth and a newborn female possesses only 1 to 2 million.
4. Within a short time from birth, all the oocytes are incorporated into follicles, but there is a steady decline in the number of follicles until menopause, when the oocyte pool is exhausted. During her reproductive life, a woman will only ovulate 400 to 500 oocytes. The other follicles are lost during any point in development through a process called atresia.

B Primordial and primary follicles

1. The primordial follicle contains a primary oocyte (arrested in meiosis I) surrounded by a single layer of squamous-shaped granulosa cells (Fig. 19–2).
2. During the initial stages of maturation, a primary follicle is formed when the granulosa layer changes into a layer of cuboidal-shaped granulosa cells, and begin to divide.
3. The follicle undergoes both a gonadotropin-independent and gonadotropin-dependent stage of development before ovulation, which takes approximately 85 days in total. However, the follicle which will ovulate in any given cycle is among the cohort of follicles which have completed the

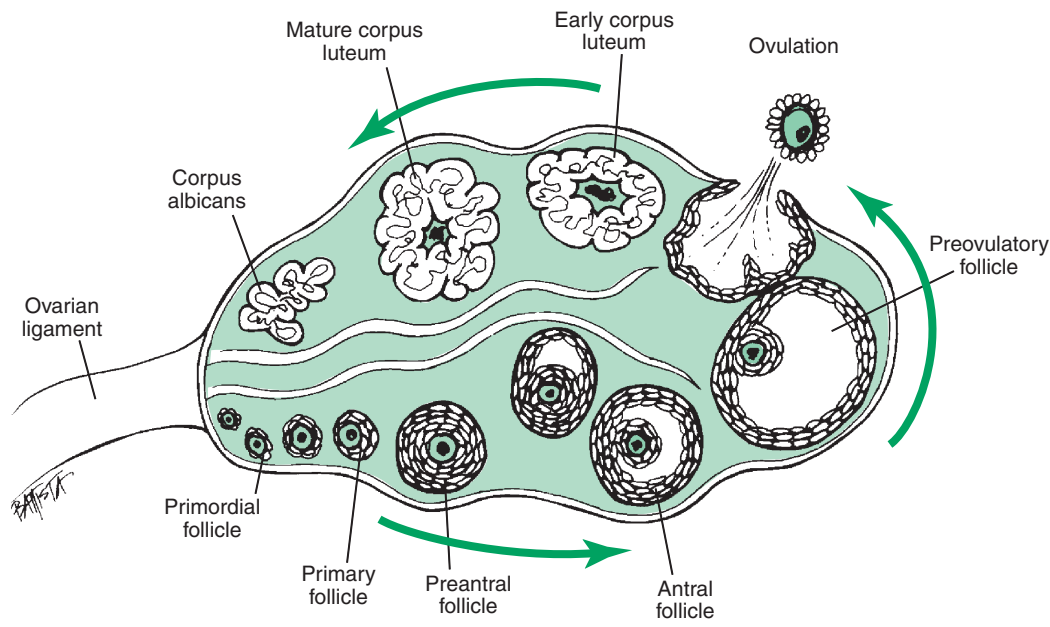


FIGURE 19-2 The process of oogenesis.

gonadotropin-independent stage of development, and are recruited during that menstrual cycle by FSH. All the other follicles in that cohort which do not ovulate will undergo atresia.

C Preantral follicle

1. The oocyte continues to grow and develops a surrounding membrane, the zona pellucida. Under the influence of FSH, the number of granulosa cells in the primordial follicle increases and forms multiple layers around the primary oocyte.
2. FSH-induced aromatization of androgen results in the production of **estrogen**, which then:
 - a. Stimulates preantral follicle growth
 - b. Together with FSH, increases FSH receptor content of the follicle
 - c. In the presence of FSH, stimulates mitosis of granulosa cells

D Antral (or Graafin) follicle

1. FSH and estrogen stimulate the development of follicular fluid, which ultimately comes together to form a cavity (or "antrum").
2. The follicle destined to become dominant secretes the greatest amount of estradiol, which, in turn, increases the density of the FSH receptors on the granulosa cell membrane.
3. Rising estradiol levels result in negative feedback and suppression of FSH release. The dominant follicle is able to respond to the decreasing concentration of FSH due to the greater number of granulosa cells within the follicle and greater number of FSH receptors per granulosa cell.
4. The other follicles in the cohort become atretic due to fewer FSH receptors, less ability to aromatize androgens to estrogens, and therefore a predominantly androgenic environment.
5. The follicular rise of estradiol exerts a positive feedback on LH secretion.
 - a. LH levels rise steadily during the late follicular phase.
 - b. LH stimulates androgen production in the theca cells.
 - c. The dominant follicle uses the androgen as substrate and further accelerates estrogen output.
6. FSH induces the appearance of LH receptors on granulosa cells.
7. Follicular response to the gonadotropins is modulated by a variety of growth factors.
 - a. **Inhibin**, secreted by the granulosa cells in response to FSH
 - (1) **Inhibin-A** under the influence of LH suppresses FSH during the luteal phase of the cycle.
 - (2) **Inhibin-B** directly suppresses pituitary FSH secretion in the follicular phase of the cycle.
 - b. **Activin** augments secretion of FSH and increases pituitary response to GnRH by enhancing GnRH receptor formation on the pituitary.

E Preovulatory follicle

1. Estrogens rise rapidly, reaching a peak approximately 24 to 36 hours before ovulation.
2. LH increases steadily until midcycle, when there is a surge, which is accompanied by a lesser surge of FSH.
3. Estradiol, which is initially inhibitory, ultimately stimulates LH release and the LH surge. This conversion is based in both an elevated level of estradiol (above 200 pg/mL) and maintenance of this level for about 2 days.
4. LH initiates luteinization and progesterone production in the granulosa cells within the follicle.
5. The preovulatory rise in progesterone causes a midcycle FSH surge by enhancing pituitary response to GnRH and facilitating the positive feedback action of estrogen.

F Ovulation (Fig. 19–3)

1. Ovulation occurs approximately 10 to 12 hours after the LH peak and 24 to 36 hours after the estradiol peak. The **onset of the LH surge**, which occurs 34 to 36 hours before ovulation, reliably indicates the timing of ovulation.
2. The **LH surge** stimulates the following:
 - a. Resumption of meiosis in the oocyte. The LH surge is responsible for overcoming the oocyte's maturation inhibitor and allowing progression of the oocyte from prophase to metaphase II by the time the oocyte (now a secondary oocyte) is released from the follicle. An oocyte can only be fertilized if it has progressed through metaphase II.
 - b. Luteinization of the granulosa cells. These luteinized granulosa cells are now able to convert cholesterol to progesterone.
 - c. Synthesis of progesterone and prostaglandins within the follicle. Prostaglandins and proteolytic enzymes are responsible for the digestion and rupture of the follicle wall leading to release of the oocyte.

G Corpus luteum

1. The ovulated follicle becomes the corpus luteum, which develops from granulosa cells that have hypertrophied, vascularized, and become filled with lipids (thus giving the corpus luteum its characteristic yellow appearance).
2. The corpus luteum produces both progesterone and estrogen, and peak levels of progesterone are attained 7 to 8 days after ovulation.
3. Normal luteal function requires optimal preovulatory follicular development.
 - a. Suppression of FSH during the follicular phase is associated with:
 - (1) Low preovulatory estradiol levels
 - (2) Depressed midluteal progesterone production
 - (3) Small luteal cell mass
 - b. The accumulation of LH receptors during the follicular phase sets the stage for the extent of luteinization and the functional capacity of the corpus luteum.
4. In the absence of pregnancy, the corpus luteum will undergo apoptosis and cease to produce progesterone by 12 to 14 days after ovulation.
5. With implantation of an embryo, which occurs approximately 7 days after ovulation, the maternal circulation is exposed to fetal human chorionic gonadotropin (hCG).
6. In early pregnancy, hCG maintains the secretion of progesterone from the corpus luteum, until placental steroidogenesis (production of progesterone) is established by about the eighth week of gestation.

V**MENSTRUATION**

- A** In the absence of a pregnancy, the demise of the corpus luteum results in decreasing estrogen and progesterone levels, which leads to increased coiling and constriction of the spiral arteries in the endometrium.

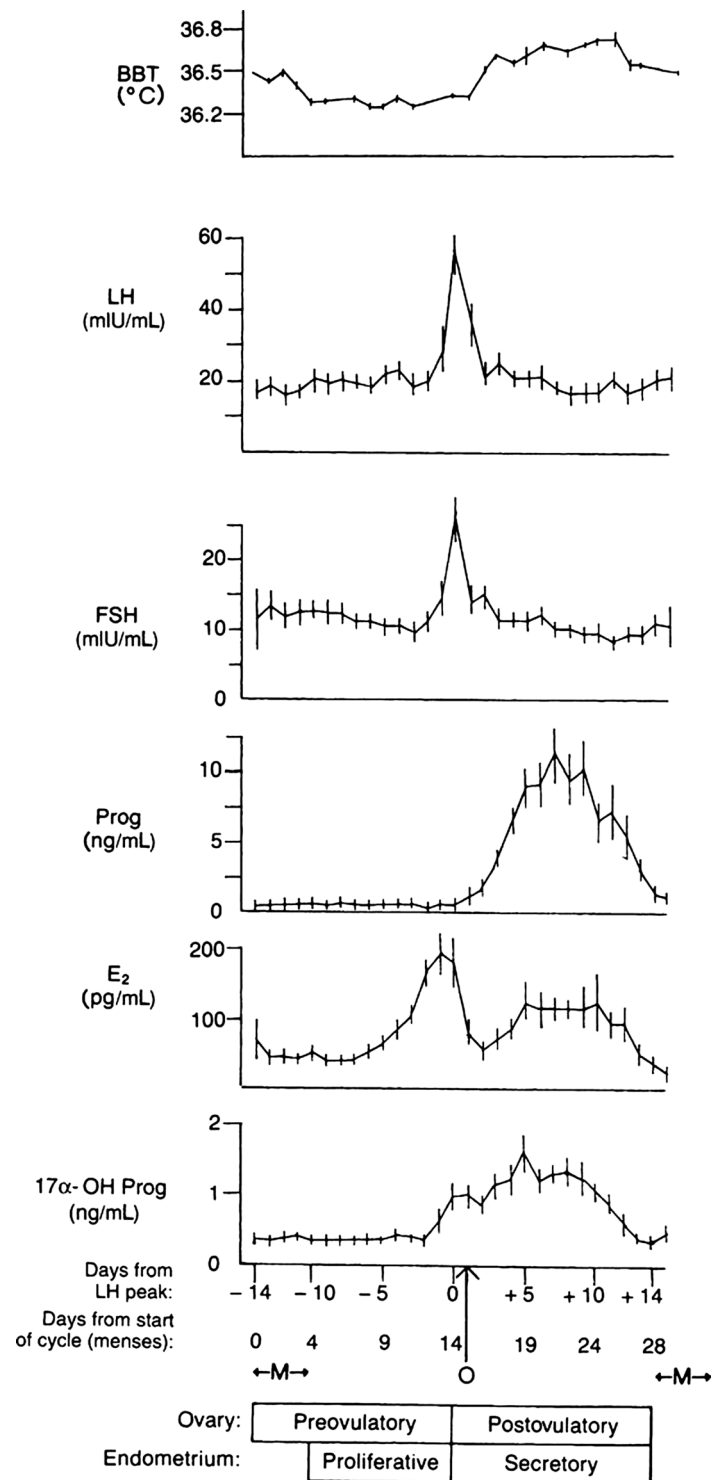


FIGURE 19-3 Hormonal (ovarian and pituitary), uterine (endometrial), and basal body temperature (BBT) correlates of the normal menstrual cycle. Mean plasma concentrations (\pm SEM) of luteinizing hormone (LH), follicle-stimulating hormone (FSH), progesterone (Prog), estradiol (E₂) [day +1], and 17 α -hydroxyprogesterone (17 α -OH Prog) are shown as a function of time. Ovulation occurs on Day 15 (day +1) after the LH surge, which occurs at midcycle on Day 14 (Day 0). M, menses; O, ovulation. (Adapted from Thorneycroft IA, Mishell DR Jr, Stone SC, et al. The relation of serum 17-hydroxyprogesterone and estradiol 17- β levels during the human menstrual cycle. *Am J Obstet Gynecol* 1971;111:947-951).

1. The decreased blood flow to the functional portion of the endometrium causes **ischemia** and degradation of endometrial tissue.
2. The bleeding, or **menses**, is the result of the degraded endometrial tissue, which is desquamated, or shed, into the uterine cavity.
3. The normal monthly menstrual flow is up to 80 mL of blood. This blood loss can lead to a lower hemoglobin in menstruating women.

B Within 2 days of the onset of menses, the surface epithelium begins to regenerate under the influence of estrogen and continues this process while the endometrium is shedding.

VI

CLINICAL PROBLEMS ASSOCIATED WITH THE MENSTRUAL CYCLE

A Dysmenorrhea Painful menses usually begins with ovulatory menstrual periods and are the most common medical problem in young women. Dysmenorrhea typically does not occur in anovulatory cycles.

1. Clinical aspects

- a. Dysmenorrhea begins just before or with the onset of menses and lasts 24 to 48 hours.
- b. The pain is suprapubic, sharp, and colicky.
- c. Nausea, diarrhea, and headache may accompany the pain.
- d. Pathologic conditions that cause dysmenorrhea must be considered in those women not responding to therapy. These include endometriosis, müllerian anomalies, and adenomyosis.

2. Physiology

- a. Menstrual cramps are the result of **uterine contractions**.
- b. **Prostaglandins** are potent **stimulators** of uterine contractions.
 - (1) Endometrial prostaglandins are produced during the luteal phase. If ovulation does not occur, there is no luteal increase in prostaglandins.
 - (2) In the first-day menstrual endometrium, the prostaglandin level increases until it is several times higher than its concentration in the luteal phase.

3. Management

- a. **Prostaglandin synthetase inhibitors** (e.g., nonsteroidal anti-inflammatory drugs) are first-line therapy because they:
 - (1) Decrease levels of endometrial prostaglandin
 - (2) Lessen uterine contractions
 - (3) Relieve dysmenorrhea best when started prior to or at the first sign of menstrual flow
- b. **Combination** (estrogen plus progestin) **oral contraceptive agents** eliminate ovulation.
 - (1) Estrogen followed by progesterone (in ovulatory cycles) is necessary to produce high menstrual levels of prostaglandin in the endometrium.
 - (2) Combination oral contraceptives prevent dysmenorrhea by eliminating the natural estrogen–progesterone progression found only in ovulatory cycles.

B Premenstrual syndrome

1. **Definition.** Premenstrual syndrome (PMS) is a group of disorders and symptoms related to the menstrual cycle. Symptoms must:
 - a. Be cyclic and have a consistent and predictable relationship to the luteal phase of the menstrual cycle, and are relieved within 4 days of the onset of menses
 - b. Be sufficiently severe to interfere with some aspects of life
 - c. Not be better explained by another diagnosis
 - d. Be present without drug, alcohol, or hormone use
2. **Epidemiology**
 - a. Eighty percent of women report some premenstrual symptoms, and 5% of women experience PMS that is severe enough to interfere with normal activities, such as work, study, parenting, or relationships.
 - b. As many as 50% to 60% of women with severe PMS have an underlying psychiatric disorder.

3. Etiology

- a. The causes of PMS are not completely understood but involve fluctuation of ovarian steroids, central nervous system neurotransmitters, genetic predisposition, and psychosocial expectations.
- b. Causal factors include estrogen, progesterone, testosterone, and neurosteroids.
 - (1) Symptoms are temporally associated with luteal-phase fluctuations in ovarian hormones. Serum levels of estrogen and progesterone are not diagnostic or predictive of PMS.
 - (2) Cyclic ovarian hormone fluctuations are associated with changes in brain neurotransmitters and neurosteroids. Changes in brain chemistry may result in PMS symptoms in biologically susceptible women.

4. Clinical manifestations. The diagnostic symptoms of PMS are divided into physical and mood-related and diagnosis includes:

- a. Physical
 - (1) Bloating or weight gain
 - (2) Breast tenderness
 - (3) Headache
 - (4) Extremity swelling
- b. Mood-related
 - (1) Anxiety
 - (2) Anger
 - (3) Irritability
 - (4) Depressive symptoms or dysphoria
 - (5) Withdrawal from social activities
 - (6) Confusion

5. Differentiation from other disorders: Many disorders may be exacerbated in the late luteal or menstrual phase of the cycle, and may have some similar symptoms to PMS. This phenomenon is known as “menstrual magnification,” and occurs in both medical conditions, such as migraines, as well as psychiatric disorders, such as depression and anxiety disorders. In disorders with overlapping symptoms, such as with depressive disorders, timing persisting outside the luteal phase can lead to the correct diagnosis.

6. Premenstrual dysphoric disorder (PMDD) differs from PMS in its pattern of symptoms, their severity, and the level of impairment (PMDD must markedly affect the social or occupational functioning of an individual).

7. PMS management (based on the guidelines of the American College of Obstetricians and Gynecologists). Both the physiologic and the psychosocial aspects of PMS must be considered when designing a therapeutic program. Most treatments for PMS are aimed at alleviating symptoms. They include:

- a. **Lifestyle changes** (i.e., regular exercise and a balanced diet, avoidance of stressful situations in the premenstrual phase of the cycle).
- b. **Calcium, magnesium, and vitamin E supplementation.**
- c. **Oral contraceptives** (more effective taken continuously) for physical symptoms. These should not be used if mood symptoms are primary.
- d. **Long-acting GnRH agonists.** These agents should be limited to short-term use because of long-term effects of hypoestrogenism and the resultant osteoporosis. Add back therapy with norethindrone or low dose estrogen/progestin may alleviate the hypoestrogenic side effects and decrease associated bone loss.
- e. **Fluoxetine and sertraline**, serotonin reuptake inhibitors. These agents can help relieve symptoms of PMS when it is taken continuously throughout the menstrual cycle, or only during the symptomatic phase.
- f. **Alprazolam**, a benzodiazepine that acts on the γ -aminobutyric acid receptor complex. This agent has been reported to be beneficial. Because of the addictive potential of alprazolam, it should be reserved for patients who can be monitored reliably and should be restricted to the luteal phase of the menstrual cycle.



Study Questions for Chapter 19

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. An 18-year-old college student presents to your office feeling depressed and irritable from 3 days prior to her menses until the day after her menses start. She reports that she frequently has to stay home from classes and is worried about its potential impact on her performance. She reports she is otherwise healthy. Menarche was at age 12, and her menses are currently regular each month. She denies significant menstrual cramping or bloating. She is sexually active with one partner, using condoms for contraception. She reports a penicillin allergy. Providing that her symptoms are prospectively documented and confirmed, what would be possible treatments for this woman?

- ☐ A Ibuprofen
- ☐ B Norgestimate plus ethinyl estradiol
- ☐ C Calcium carbonate
- ☐ D Leuprolide
- ☐ E Only answer A would not be an appropriate therapy

2. During in vitro fertilization, medical stimulation causes multiple follicles to develop to the stage of ovulation, rather than just one dominant follicle. What hormone is responsible for this multifollicular development?

- ☐ A Estradiol, because the high estrogen environment supports the growing follicles
- ☐ B FSH, because the high FSH levels support the growing follicles
- ☐ C LH, because the LH induces steroid production which provides more substrate for the granulosa cells in the smaller follicles to produce estradiol locally to support their growth
- ☐ D Estradiol, because the high estrogen levels initially provide negative feedback to the hypothalamus, postponing the LH surge and allowing more follicles to grow
- ☐ E FSH, because the FSH selectively downregulates the LH receptors in the dominant follicle, giving the smaller follicles a selective advantage

3. A 41-year-old woman presents to your office with perimenopausal symptoms. She had two children, both by IVF, and had undergone several cycles prior to becoming pregnant with her children. She learned from her niece, a medical student, that all women are born with a finite number of eggs, and that when they are gone, you undergo menopause. She remembers that with each IVF cycle, over 20 eggs were removed from her body and is worried that she has severely depleted her supply. She is worried about undergoing menopause early. You tell her:

- ☐ A That you will start her on oral contraceptive pills to slow down loss of follicles each month and boost her ovarian reserve
- ☐ B She did not ovulate during the time when she was pregnant, so this will counterbalance any decline IVF caused
- ☐ C That IVF did not affect the number of follicles remaining in her ovaries
- ☐ D That IVF did decrease the number of follicles she has remaining, but currently there is no treatment for this

4. During the follicular phase, hormone X provides negative feedback and suppresses FSH expression from the pituitary. Hormone Y is responsible for stimulation of the LH surge. Hormone Z is responsible for the conversion of primary oocytes to secondary oocytes.

- ☐ A Hormones X and Y are the same
- ☐ B Hormones Y and Z are the same
- ☐ C Hormones X and Z are the same
- ☐ D Hormone X is Inhibin-A
- ☐ E Hormone Y is Activin



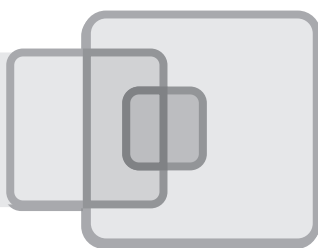
Answers and Explanations

1. **The answer is C** [VI B 6]. The clinical scenario presented here is describing PMS. Calcium supplementation is one therapy that may be of use to this patient and is the best answer given. Nonsteroidal anti-inflammatory agents (ibuprofen) are used to treat dysmenorrhea, not PMS. Hormonal contraception (norgestimate plus ethinyl estradiol) is indicated for PMS with primarily physical symptoms which would not be appropriate in this patient as she denies significant physical symptoms. Leuprolide would suppress menstrual cycles and is a treatment for PMS, but is associated with significant side effects and would not be a first-line therapy. Lifestyle changes and serotonin reuptake inhibitors are other potentially appropriate therapies for this patient.

2. **The answer is B** [IV D 2 to 4]. During a natural cycle, the decline in FSH secretion from the pituitary as a result of negative feedback is key to the development of a dominant follicle since only the dominant follicle, and not smaller follicles, is able to continue to grow in the setting of lower FSH. During an IVF cycle, excess FSH is given so all the follicles are exposed to adequate stimulation to grow and develop. There is no negative feedback with the pituitary decreasing the FSH concentration. FSH increases, not decreases, the LH receptors on the dominant follicle. Estradiol is produced by the growing follicles and giving excess estrogen would not support their growth nor would it postpone the LH surge. LH does induce steroid production, providing substrate for conversion to estradiol, but excess LH would trigger ovulation.

3. **The answer is C** [IV A4, B3]. Ovarian reserve is primarily a function of age (time). Follicular atresia occurs *independent* of gonadotropin stimulation. In a normal menstrual cycle, multiple follicles are primed to respond to FSH produced at the beginning of the cycle, but because of negative feedback from estradiol on FSH, only one usually matures and ovulates, the rest becoming atretic. With IVF, high doses of FSH are given to facilitate growth of all potential follicles that are primed at that time, in essence rescuing multiple follicles from atresia rather than destroying more follicles/oocytes than would be otherwise. There is continuous growth and atresia of primordial follicles occurring from fetal life through menopause. Pregnancy and oral contraception (i.e., anovulation) do not stop this process—menopause cannot be delayed by using oral contraceptives. Therefore, women lose a certain number of their follicles every month whether they ovulate or not. Follicular atresia can be increased by chemotherapy and radiation used for treatment of cancer as these agents destroy the oocytes.

4. **The answer is A** [IV D3, D7, E3]. Hormone X could be either Inhibin-B or estradiol, both of which provide negative feedback and suppress FSH expression in the follicular phase. Inhibin-A suppresses FSH in the luteal phase, and therefore is not hormone X. Hormone Y is estradiol, which is an important factor in triggering the LH surge (and converts from inhibitory to stimulatory). Activin augments secretion of FSH, but it is not responsible for the LH surge. Hormone Z is LH. LH is responsible for the release of primary oocytes from prophase I, with their resultant conversion to secondary oocytes arrested in metaphase II. The only correct answer is that hormone X and hormone Y are the same: that is, both are estradiol.



Pediatric and Adolescent Gynecology

SULEENA KANSAL KALRA • DIANA CHAVKIN • SAMANTHA M. PFEIFER

I

INTRODUCTION

An awareness of the problems that are unique to pediatric and adolescent gynecology is invaluable for proper management of the young patient. Particular care is essential in addressing gynecologic concerns in this age group because both physical and emotional trauma may be inadvertently inflicted. It is important to establish rapport and reassurance in a young patient who may be uncomfortable with pelvic or genital examinations. A female adolescent does not need a pelvic examination unless she is experiencing abnormal symptoms. Even then, noninvasive imaging (e.g., pelvic ultrasound and magnetic resonance imaging [MRI]) can be performed instead of a pelvic examination. Once an adolescent is sexually active, a regular pelvic examination is indicated.

A Normal findings in a pediatric patient include the following:

1. A mucoid vaginal discharge and even vaginal bleeding in an infant for up to 2 weeks after birth; caused by maternal estrogens
2. An introitus that is located more anteriorly than normal and a clitoris that is more prominent than normal (1 to 2 cm)
3. A redundant hymen that may protrude on straining and that remains essentially the same size until 10 years of age
4. A vaginal epithelium that is uncornified and erythematous with an alkaline pH
5. A small uterus (2.5 to 3 cm in length), with the cervix comprising two-thirds of the organ (the reverse of adult proportions)
6. A cervical os that is covered with glandular epithelium and normally appears red (ectropion)

B Normal findings in an adolescent patient

1. Intact hymen in those not sexually active
2. Postpubertal gynecologic examination in an adolescent is similar to an adult female

C Visualization of the vagina Instruments for visualizing the vagina include the vaginoscope, the urethroscope, and the pediatric speculum. Stirrups are usually not necessary for the preadolescent; a simple “frog-leg” position is usually sufficient. Occasionally, intravenous sedation may be necessary to accomplish a thorough genital examination. To determine the presence or absence of internal genitalia, ultrasound and MRI are helpful.

D Rectal examination is often more informative than a vaginal examination because the short posterior vaginal fornix cannot be distended and a cul-de-sac does not exist.

II

VULVOVAGINAL LESIONS

A Lichen sclerosus et atrophicus

1. **Clinical picture.** The child will usually present with vulvar itching and/or discomfort. A hypopigmented lesion may cover the vulvar and perianal regions in an hourglass shape and punctate

hemorrhages may be seen. As the disease progresses, there may be loss of normal architecture, including loss of demarcation of the labia and scarring of the clitoral hood.

2. **Etiology.** Causes are unknown, though hypoestrogenic state is thought to play a role.
3. **Diagnosis.** In children, visual inspection is used to make the diagnosis. Biopsy, which shows superficial hyperkeratosis with basal atrophic and sclerotic changes in adults, is rarely indicated in the pediatric population.
4. **Management.** This condition is benign and can be self-limiting. Improved hygiene is the first line of therapy. Low-potency topical steroid cream is not usually effective. High-potency topical steroid (Clobetasol 0.05% ointment) is used to treat the condition. Initial treatment starts with twice daily application for 2 weeks and the patient should be reassessed after 2 weeks to determine response to treatment. Treatment duration is usually 6 to 12 weeks: once signs and symptoms of disease resolve, steroids should be slowly tapered to avoid a rebound effect. Untreated lichen sclerosis can lead to scarring, loss of anatomy, and resultant sexual dysfunction. It may resolve at puberty but is usually chronic.

B Trauma

1. Clinical picture

- a. **Tears, abrasions, ecchymoses, and hematomas** are common in preadolescent girls. The incidence is highest in children between 4 and 12 years of age. The most common mechanisms of injury are sexual abuse, straddle injuries, accidental penetration, sudden abduction of the extremities, and pelvic fractures. Most genital trauma results from straddle injuries, such as a child landing on the center bar of a boy's bicycle. The injury may appear as a small ecchymotic area or a large vulvar hematoma. The clinician must always suspect sexual abuse when a child presents with genital trauma.
- b. **Sexual abuse** necessitates immediate medical attention, including a complete physical examination, cervical and rectal smears, serologic tests, and psychological evaluation and follow-up. Genital findings, when present, should be recorded very carefully because of their importance in supporting allegations of abuse in court proceedings. The colposcope is used to document specific normal and abnormal findings, and photographs can be placed in the patient's chart. However, in cases of sexual abuse, 96% of patient abnormalities are detected with the unaided eye.

2. Management

- a. When vaginal bleeding occurs because of pelvic trauma, **a complete and thorough examination is mandatory.** This includes evaluation of the urinary system and rectum. A vaginoscope is used to visualize the vagina to locate sources of bleeding. A large vaginal laceration may result in an expanding hematoma in the retroperitoneal space. Superficial abrasions and lacerations of the vulva, if not actively bleeding, can be cleaned and left alone. If adequate visualization cannot be performed, examination under anesthesia is required.
- b. **Conservative therapy** for most traumas consists of rest, ice, and analgesics.
- c. In sexual abuse, **antibiotic therapy** is advised as prophylaxis against sexually transmitted diseases. Current Centers for Disease Control and Prevention (CDC) recommendations (2006) include treatment with either: (a) ceftriaxone + metronidazole + azithromycin or (b) doxycycline for pelvic infections. Hepatitis B vaccination is indicated if the patient has not been previously vaccinated.

C Labial agglutination

1. **Clinical picture.** Adhesion of the labia minora in the midline is the usual presentation. This vertical line of fusion distinguishes labial agglutination from imperforate hymen or vaginal atresia. Labial agglutinations can be asymptomatic, or result in retention of urine and/or vaginal secretions and can lead to vulvovaginitis or urinary tract infections. The adhesion may be complete or partial, involving only the upper or lower portion of the labia. The etiology of labial adhesions is unknown.

2. Management

- a. If asymptomatic, **improved hygiene** may be all that is necessary. The adhesions may resolve when estrogen production increases at puberty. Treatment is indicated if the adhesions are causing difficulty urinating or recurrent infections.

- b. **Topical estrogen** (conjugated equine estrogens or estradiol cream) applied twice daily directly to the adhesion, induces cornification of the epithelium, and promotes spontaneous separation. The formation of breast buds is a rare side effect of topical estrogen and will resolve after treatment is discontinued. The majority of labial adhesions will resolve after 6 weeks of correct topical treatment.
- c. **Surgical separation** is rarely necessary and reserved for cases with complete urinary obstruction or those who fail medical treatment. Surgical treatment requires sedation or analgesia and should be followed by 1 to 2 weeks of postoperative treatment with topical estrogen cream. **Continuation of nightly emollient application such as petroleum jelly can be useful to avoid recurrences.**

D Prolapsed urethra

1. **Clinical picture.** A small, hemorrhagic, friable mass surrounding the urethra causing painless bleeding, dysuria, or difficulty with urination is the most common presentation. The average age at diagnosis is 5 years. The lesion can easily be confused with a condyloma but can be distinguished by applying a dilute acetic acid solution: a condyloma turns white, whereas a prolapsed urethra remains pink and fleshy.
2. **Management**
 - a. Topical estrogen cream will result in resolution of prolapse in the majority of cases. Initial treatment begins with twice daily application for 2 weeks and the urethra is then reassessed. Treatment is continued until the prolapse has resolved. Usually a few weeks of treatment are necessary. Even in cases with necrosis of the distal urethra, topical treatment will generally be effective and surgery is rarely indicated. If medical treatment fails to correct the prolapse, a urethral polyp should be considered.
 - b. If urinary retention or necrosis is present, **surgical repair** and catheterization are necessary.

E Vaginal discharge

1. **Clinical picture**
 - a. A **mucoid discharge** is common in infants for up to 2 weeks after birth; it results from maternal estrogen. It is also a common finding in prepubertal and postpubertal girls, who experience increased estrogen production by maturing ovaries.
 - b. **Pathologic discharge** may result from any of the following conditions:
 - (1) **Infections with organisms**, such as *Escherichia coli*, *Proteus*, *Pseudomonas*, Pinworm, yeast, *Gardnerella*, *Neisseria gonorrhoeae*, *Chlamydia*, and *Trichomonas*
 - (2) **Hemolytic streptococcal vaginitis**, which results in a bloody or serosanguineous discharge, usually after a streptococcal infection elsewhere (e.g., skin or throat)
 - (3) **Monilial vaginitis**, which is common in children with diabetes or after antibiotic therapy
 - (4) **A foreign body**, which can cause persistent vaginal discharge, sometimes with pain and bleeding
 - (5) **Nonspecific vaginitis** from local irritation, scratching, manipulation, or poor hygiene
2. **Management.** Conservative management is advisable, as follows:
 - a. **Culture** to identify causative organisms. Preliminary search for *Monilia*, nonspecific bacteria, and *Trichomonas* can be accomplished by examining the discharge on a laboratory slide with saline and sodium hydroxide (20%) preparations added.
 - b. **Urinalysis** to rule out cystitis.
 - c. **Review proper hygiene.** Instruct the child's caretaker to avoid placing the child in tight clothing or using perfume soaps, bubble bath, and powders. The child should avoid prolonged periods in moist clothing.
 - d. **Perianal examination** with transparent tape to test for pinworms.
 - e. **In cases of persistent discharge, examination under anesthesia is indicated to rule out foreign body.**

III

NEOPLASMS

- A** **Tumors of the vagina**, although uncommon, are most often malignant. **Sarcoma botryoides** is the most common malignant vaginal tumor.

1. Clinical picture

- a. Sarcoma botryoides arises from mesenchymal tissue of the cervix or vagina, usually on the anterior wall of the upper vagina. It grows rapidly, fills the vagina, and then protrudes through the introitus.
- b. It appears as an edematous, grape-like mass that bleeds readily on touch. It is usually multicentric and extension is usually local, with rare instances of distant metastases.

2. **Management.** A combination of surgery and chemotherapy is most commonly used.

B Ovarian tumors

1. **Clinical picture.** Although uncommon in children, ovarian tumors may present as torsion (twisting) of the ovaries. Among ovarian neoplasms, 40% are of nongerm cell origin (coelomic epithelium), and 60% are of germ cell origin. Most ovarian neoplasms in adolescents are also endocrine secreting regardless of origin.

a. Nongerm cell origin

- (1) Lipoid cell tumors (estrogen producing)
- (2) Granulosa-theca cell tumors (estrogen producing), of which approximately 20% are malignant

b. Germ cell origin

- (1) Benign cystic teratomas
- (2) Benign cysts
- (3) Arrhenoblastomas (androgen producing)
- (4) Dysgerminomas and gonadoblastomas (tumors of dysgenetic gonads)
- (5) Endodermal sinus tumors
- (6) Embryonal carcinomas (human chorionic gonadotropin [hCG]-secreting tumors)
- (7) Immature teratomas, which account for 20% of malignant germ cell tumors

2. **Therapy. Treatment is surgical**, alone or in combination with chemotherapy, depending on the tumor. Radiation is sometimes used to treat dysgerminomas.

IV

CONGENITAL ANOMALIES IN THE PEDIATRIC PATIENT

A Müllerian agenesis (Mayer–von Rokitansky–Kuster–Hauser [MRKH] syndrome) Vaginal and uterine agenesis (atresia) represents a failure of the caudal müllerian duct to fuse with the urogenital sinus.

1. Clinical picture

- a. This condition most often is diagnosed at the time of puberty because of the resulting amenorrhea. **Ovarian development is normal**, but there is only a vaginal dimple at the introitus and the **uterus is usually absent or fails to develop** beyond a rudimentary structure. The rudimentary uterus may have functioning endometrium which causes pain with shedding during the menstrual cycle. The incidence of MRKH is 1/5,000.
- b. Vaginal agenesis (normal 46,XX karyotype) must be distinguished from androgen insensitivity syndrome (AIS; male 46,XY karyotype), which is also associated with an absent vagina.
- c. Since ovarian development is usually normal, these patients develop normal secondary sexual characteristics (breast development, axillary, and pubic hair).
- d. Associated urologic anomalies are common (20%) and include unilateral renal agenesis, pelvic or horseshoe kidney, and irregularities of the collecting system.

2. **Evaluation.** Physical examination should focus on presence of secondary sex characteristics and presence of axillary and pubic hair to distinguish from AIS. Absence of vagina and assessing the external genitalia should be determined by examination. A rectal examination can confirm absence of vaginal mass. Pelvic ultrasound is helpful in determining if the uterus is present and excluding other diagnoses such as imperforate hymen which is associated with a large hematocolpos. Pelvic MRI may be necessary for confirmation or to evaluate for remnant uterine structures, especially when there is cyclic pain. Renal ultrasound is recommended to evaluate the kidneys.

3. **Treatment is deferred until after puberty** when the patient has a good understanding of the condition and is emotionally ready to consider treatment.
 - a. **Creation of a neovagina**
 - (1) **Nonsurgical treatment with self-dilation techniques is the preferred approach.**
 - (2) Surgical approaches involve creating a space between the rectum and vagina and lining with graft tissue (McIndoe procedure), pelvic peritoneum (Davydov procedure), or using a traction device to lengthen the vagina from above (Vecchiotti procedure).
 - b. **Although these women cannot carry a pregnancy due to uterine abnormalities, they can have oocytes retrieved for in vitro fertilization and have embryos transferred to a gestational carrier.**
 - c. Counseling is often needed to help address emotional issues related to lack of ability to carry a pregnancy and feelings of being “different.”

B Ectopic ureter with vaginal terminus

1. **Clinical picture**
 - a. Ectopic ureter is a condition in which the ureter terminates in a site other than the bladder as it normally should. The most common site for ureter termination in girls is the vagina. This is the most common cause of vaginal cysts in infants, presents as a **ureterocele**, which appears as a cystic mass protruding from the vagina. If the ureter is patent, constant irritation and vaginitis may result.
 - b. The ectopic ureter is usually a result of a duplicated renal collecting system, a duplex kidney with two ureters. One ureter drains correctly to the bladder while the duplicated/ectopic ureter usually drains the rudimentary upper renal pole of the kidney.
 - c. Urinary incontinence, recurrent urinary tract infections, **hydroureter**, and **hydronephrosis** may develop.
2. **Diagnosis.** The existence of an ectopic ureter is made using **intravenous pyelography**, which allows visualization of the entire urinary tract.
3. **Management.** It is preferable to **resect the lowest portion of the ureter and implant it into the bladder** rather than remove the ureter and the associated portion of the kidney.

C Vaginal ectopic anus

1. **Clinical picture.** Vaginal ectopic anus is an **imperforate anus associated with rectovaginal communication**. Only a skin dimple is found at the normal anal site.
2. **Management.** **Surgical correction** is indicated.

V

DISORDERS OF SEXUAL DEVELOPMENT (AMBIGUOUS GENITALIA)

Ambiguous genitalia results when hormones with androgenic activity are present during development of a female fetus, or androgens or androgen activity are absent during development of a male fetus. The resulting appearance of the genitalia can be incomplete, or a mixture of male and female features, making identification of sex difficult at birth. Early diagnosis is important to counsel the parents about the cause of the developmental disorder and facilitate planning for assignment of sex to minimize psychological problems and to allow for gender role assignment. Traditionally this has been done in the neonatal period, but there are some conditions where delaying gender assignment may be better. This field is evolving.

- A Congenital adrenal hyperplasia (CAH) is the most common cause of distinct virilization of the female newborn** It is caused by the impairment of enzymatic functions that are crucial in the steps in the breakdown of cholesterol to form cortisol and aldosterone. When cortisol production is decreased there is less negative feedback to the pituitary and adrenocorticotrophic hormone (ACTH) secretion is subsequently increased. Both the precursors immediately preceding the impaired step and the byproducts have biologic activity, predominantly androgenic than can lead to the clinical and biochemical features observed. **The most common enzyme defect responsible for CAH is the 21-hydroxylase defect (CYP21A2)**, less common defects include 11-hydroxylase defect and 3- β hydroxysteroid defect. The incidence of 21-hydroxylase defect is 1 in 5,000 births, and it accounts for 95% of all cases of CAH, which is inherited as an **autosomal recessive trait**.

1. **Clinical picture.** The chromosomes, gonads, and internal genitalia are female, but the external genitalia are virilized to varying degrees. The degree of closure of the urogenital orifice varies, and clitoral enlargement and accentuation of labial folds are characteristic. The disorder is progressive if untreated.
2. **Diagnosis.** Serum 17-hydroxyprogesterone (17OHP) and dehydroepiandrosterone (DHEA) obtained after 24 hours of life are both elevated as these hormones are immediate precursors for the defective 21-hydroxylase enzyme and therefore will accumulate. A blood karyotype should be obtained. **Serum electrolytes should be obtained at birth and followed because of salt wasting, which can be life-threatening, may occur.**
3. **Management**
 - a. Glucocorticoid (usually hydrocortisone) is administered indefinitely to all patients. Treatment reduces the excessive corticotropin-releasing hormone (CRH), ACTH secretion, and resultant hyperandrogenism so that growth, sexual maturation, and eventual reproductive function are normal.
 - b. Mineralocorticoid (usually fludrocortisone) is given to restore serum electrolyte concentrations and extracellular fluid volume to normal in the salt-wasting form of the disorder.

B Adrenal tumors These tumors, which may cause virilization of the external genitalia after infancy, should be suspected in children with high levels of dehydroepiandrosterone sulfate (DHEAS).

C Maternal ingestion of androgenic substances This condition can result in **masculinization of the female fetus**. Causal agents identified include androgens, danazol, and synthetic progestins (in doses much higher than in oral contraceptive pills).

1. **Clinical picture.** Masculinization is limited to the external genitalia. The clitoris is enlarged and the labia may be fused, but the vagina, tubes, and uterus are normal. Growth and development are normal, and progressive virilization does not occur.
2. **Diagnosis.** The condition can be diagnosed on the basis of a positive history and on exclusion.
3. **Management.** Clitoral reduction and surgical correction of the fused labia may be necessary.

D Childhood ingestion of androgens This condition usually involves preparations that have androgenic activity.

1. **Clinical picture.** Clinical manifestations are the same as those resulting from maternal ingestion of androgenic substances (i.e., masculinization; see V C 1).
2. **Management.** Therapy involves clitoral reduction and surgical correction of the fused labia, if necessary.

E Androgen insensitivity syndrome (testicular feminization)

1. **Clinical picture.** A 46,XY genotype is present, but a female phenotype develops.
 - a. Androgens are produced by the testes (which develop in the presence of a Y chromosome) and by the adrenal glands. A defect in the androgen receptor prevents tissue from responding to androgen stimulation.
 - b. External genitalia are feminized because normal (male) development of these structures is prevented by lack of response to dihydrotestosterone, which is the androgen that masculinizes target tissues. These infants appear as normal females at birth, and are reared as girls. In the incomplete form of the syndrome, there is some response to the circulating androgens, and ambiguous genitalia may occur.
 - c. The testes produce müllerian inhibitory substance (MIS); as a result, there is no development of the uterus, cervix, upper vagina, or fallopian tubes. A short vagina that ends in a blind pouch and labia, which often contains testes, develops in these patients.
 - d. Lack of responsiveness to testosterone during embryonic sexual differentiation affects development of internal genitalia. Normal male internal genitalia do not develop because testosterone is required for that process to occur.
 - e. An incomplete form (Reifenstein syndrome) occurs in which external genitalia appear virilized.
2. **Diagnosis.** Patients with complete AIS are usually diagnosed at puberty with primary amenorrhea and a blind or absent vagina. Because of the inability to respond to androgens, there is lack

of pubic and axillary hair development. **Breast development does occur because estrogen concentration is high due to conversion of testosterone (by the enzyme aromatase) produced after puberty.** This syndrome is distinguished from müllerian agenesis by absent axillary and pubic hair development and a high testosterone level. A karyotype should be performed for confirmation.

3. **Management.** The gonads should be removed because of an increased risk of malignancy (3% to 4% before 25 years of age). However, removal should be performed **after** puberty to allow for appropriate growth and development.

F True hermaphroditism

1. **Clinical picture.** The genotype of most true hermaphrodites is 46,XX. The external genitalia may appear male, female, or ambiguous. Both male and female internal genitalia may be present. Sex assignment and rearing should be consistent with the dominant appearance of the external genitalia and with surgical correctability.
2. **Management.** The genitalia that are inconsistent with sex assignment should be surgically removed or modified.

- G Maternal virilizing tumor during pregnancy** (luteoma of pregnancy). This condition may result in masculinization of the female fetus. The clinical picture and therapy are similar to those for the maternal ingestion of androgenic substances (see V C). Psychological development and mental capacity are consistent with chronologic age. Reproductive potential is not adversely affected, and the patient can become pregnant.

VI

NORMAL AND ABNORMAL PUBERTAL DEVELOPMENT

- A Normal puberty** Puberty encompasses the psychological, physical, and endocrinologic changes beginning in late childhood that ultimately allow for reproductive capacity. In North America, the average age of onset of puberty in girls is 9 years. Once initiated, it proceeds over an average of 4 to 5 years and culminates in the onset of menses. Secretion of GnRH from the hypothalamus is felt to be responsible for initiating pubertal changes. Although the exact mechanism responsible for turning on the hypothalamus has yet to be elucidated, factors identified as influencing this process include: race/genetic factors with African Americans having an earlier onset than non-Hispanic Caucasians, better nutrition, environmental toxic exposures to hormones including estrogens in poultry, phthalates in plastics, and regulatory factors such as GABA, neuropeptide Y, leptin, and kisspeptin.
- B** The normal physical changes associated with puberty in girls were studied and outlined in detail by two British physicians in the late 1960s, Marshall and Tanner. Their work resulted in the Tanner stages of breast and pubic hair development. Tanner stages are currently used to evaluate pubertal development in children (Table 20–1). Components of the normal puberty include the following:
 1. **Growth spurt.** The growth spurt begins before the onset of other signs of puberty. The peak growth velocity occurs at an average age of 11 to 12 years, usually 1 year before menarche.
 2. **Thelarche.** The onset of breast development usually begins between 9 and 11 years of age. It is a sign of ovarian estrogen production and is completed over approximately 3 years. Tanner stages describe the normal changes in the transition from the prepubertal to the mature breast contour (Fig. 20–1).
 3. **Adrenarche and pubarche.** Adrenarche refers to the production of androgens from the adrenal gland, and pubarche is the development of axillary and pubic hair that results from the adrenal and gonadal androgens. Adrenarche is not regulated by the same hypothalamic–pituitary process that governs the rest of puberty. Pubarche usually follows thelarche in the pubertal sequence but can be the first sign of puberty in up to 20% of girls. Again, Tanner stages are used to describe normal pubic hair development (Fig. 20–2).
 4. **Menarche.** With menarche, vaginal bleeding occurs for the first time in response to hormonal changes, specifically production of estrogen by the ovary. The average age of the first menses is 12 to 13 years. For the first 2 years following menarche, menses are often irregular because of anovulation or sporadic ovulation.

TABLE 20–1 Tanner Staging

	Breast	Pubic Hair
Stage 1 (prepubertal)	Elevation of papilla only	No pubic hair
Stage 2	Elevation of breast and papilla as small mound; areola diameter enlarged; median age: 9.8 years	Sparse, long, pigmented hair chiefly along labia majora; median age: 10.5 years
Stage 3	Further enlargement without separation of breast and areola; median age: 11.2 years	Dark, coarse, curled hair sparsely spread over mons; median age: 11.4 years
Stage 4	Secondary mound of areola and papilla above the breast; age: 12.1 years	Adult-type hair, abundant but limited to mons; median age: 12 years
Stage 5	Recession of areola to contour of breast; median age: 14.6 years	Adult-type spread in quantity and distribution; median age: 13.7 years

Adapted with permission from Speroff L, Glass RH, Kase NG. Clinical Gynecologic Endocrinology and Infertility. 6th Ed. Philadelphia: Lippincott Williams & Wilkins, 1999:397.

C Precocious puberty This condition is characterized by the onset of secondary sexual characteristics before 8 years of age in Caucasian girls and before 7 years of age in African American girls. Besides the psychological ramifications inherent in this syndrome, there exists the risk of short stature from early epiphyseal closure. Most cases of precocious puberty are idiopathic.

1. Forms of precocious puberty

- a. **Central precocious puberty (gonadotropin-dependent precocious puberty).** This type of precocious puberty is caused by early activation of the hypothalamic–pituitary–gonadal axis, leading to the onset of hormonal secretion from the ovaries. The most common cause is idiopathic (74%). Other causes are rare and include central nervous system lesions such as infection, craniopharyngioma, astrocytoma, neurofibroma, hemangioma of the hypothalamus, hydrocephalus, and neoplasm of the floor of the third ventricle.

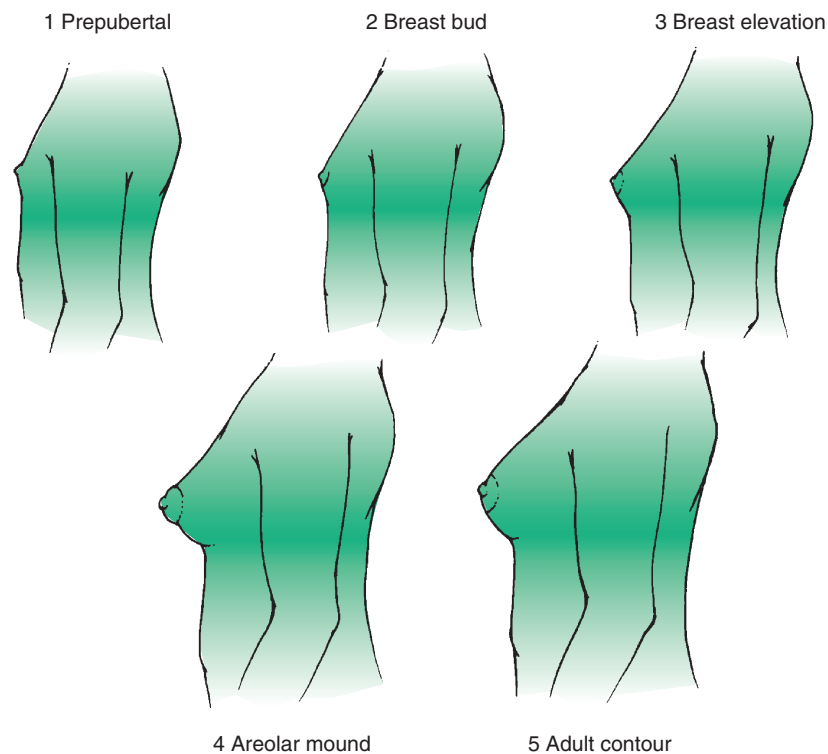


FIGURE 20–1 Tanner stages of normal breast development. (Adapted from Speroff L, Glass RH, Kase NG. Clinical Gynecologic Endocrinology and Infertility. 6th Ed. Philadelphia: Lippincott Williams & Wilkins, 1999:398).

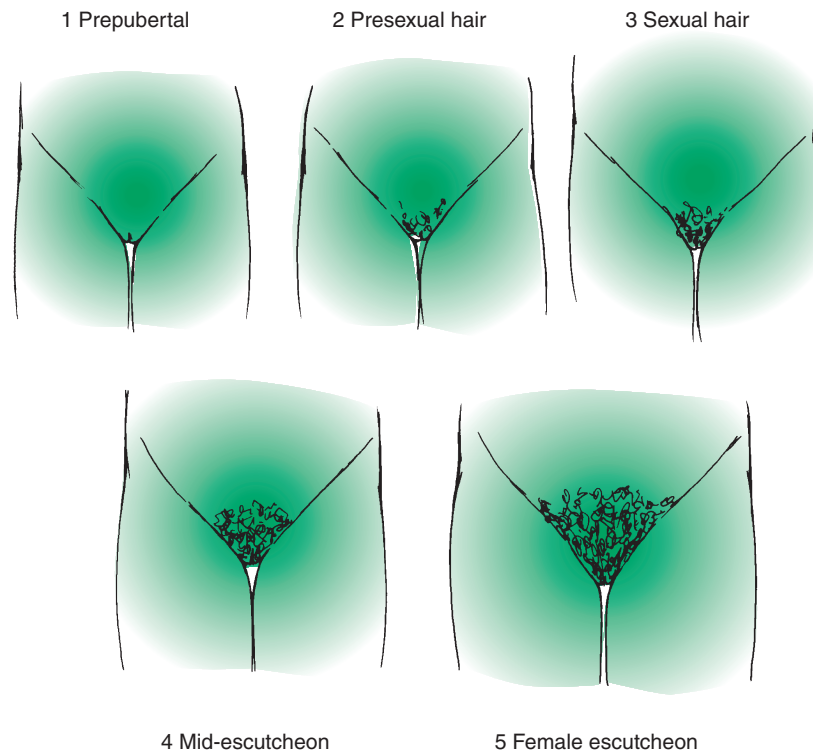


FIGURE 20-2 Tanner stages of normal pubic hair development. (Adapted from Speroff L, Glass RH, Kase NG. *Clinical Gynecologic Endocrinology and Infertility*. 6th Ed. Philadelphia: Lippincott Williams & Wilkins, 1999:399).

b. Peripheral precocious puberty (gonadotropin-independent precocious puberty). This type of precocious puberty is caused by secretion of sex steroids from the ovary or exogenous hormone ingestion. These include hormone-producing ovarian or adrenal tumors, McCune–Albright syndrome (triad of peripheral precocious puberty, café-au-lait skin pigmentation, and fibrous dysplasia of bone), ectopic gonadotropin production, and primary hypothyroidism.

2. **Diagnosis.** Physical and radiologic signs are the basis of diagnosis. Assessment of bone age is critical, usually with a plain film of the wrist of the nondominant hand. An endocrine profile including gonadotropin levels and thyroid function tests must be evaluated. In addition, imaging of the brain with computed tomography (CT) or MRI is essential to rule out an intracranial mass.
3. **Management.** Therapy is aimed at slowing down accelerated growth; reducing pituitary, ovarian, and adrenal function; and inducing regression of secondary sex characteristics. **For idiopathic precocious puberty, the treatment of choice is gonadotropin-releasing hormone (GnRH) agonists, which suppress the pituitary and halt the progression through puberty.** The treatment is continued until an appropriate age has been reached for resumption of pubertal development. In cases of known etiology, recommended therapy is with surgery, chemotherapy, or radiation therapy as indicated.

D Delayed puberty Delayed puberty is characterized by the absence of breast development by the age of 13 years or the absence of menses by the age of 16 years.

1. Categories

- a. **Hypergonadotropic hypogonadism.** This condition affects almost 50% of all patients with delayed puberty. It includes conditions in which the ovaries or gonads are not functioning and are unable to respond to gonadotropins; as a result, gonadotropin levels are high. Examples include Turner syndrome (45,X), idiopathic premature ovarian failure, autoimmune ovarian failure, gonadal dysgenesis, and ovarian failure secondary to radiation therapy or chemotherapy.
- b. **Hypogonadotropic hypogonadism.** This condition accounts for 10% to 15% of patients with pubertal delay. The ovary is normal; however, there is a lack of production of hormonal

stimulation from the hypothalamus. Hypogonadotropic hypogonadism includes Kallmann syndrome (isolated GnRH deficiency); hypothalamic suppression by stress, severe disease, or malnutrition; and tumor invasion of the pituitary (prolactinoma or craniopharyngioma).

- c. **Eugonadotropic.** Constitutional delay accounts for 10% to 20% of cases. These patients have normal progression of the stages of puberty; the initiation of the process is simply delayed.
2. **Management.** Treatment is based on the etiology of the delay. In cases of gonadal dysgenesis when a Y chromosome or fragment of a Y chromosome is present, the gonads should be removed at diagnosis because of the risk of neoplastic degeneration. Otherwise, hormone replacement with estrogen, and subsequently both estrogen and progesterone, is required to promote sexual development and menarche.

VII

SPECIAL PROBLEMS OF THE ADOLESCENT

A Dysmenorrhea is defined as cramp-like pain in the lower abdomen associated with menstrual flow.

1. **Etiology**
 - a. **Primary dysmenorrhea** accounts for most cases and is attributed to increased prostaglandin production with menses in the presence of normal anatomy.
 - b. **Secondary dysmenorrhea** results from conditions such as endometriosis and müllerian anomalies with an obstruction in a portion of the outflow tract, which leads to pain in the obstructed segment, but menstrual flow is not affected. Examples include obstructed hemiuterus and uterus didelphys with obstructed hemivagina.
2. **Clinical picture.** Severe, cyclic, cramp-like pain located in the lower abdomen and pelvis is associated with menses. Pain may radiate to the thighs and back and be accompanied by nausea, vomiting, and diarrhea.
3. **Management.** First-line therapy is prostaglandin inhibitors (nonsteroidal anti-inflammatory drugs [NSAIDs]). If the symptoms are not adequately controlled, then the next step is to empirically start oral contraceptives or obtain a pelvic ultrasound to evaluate for abnormal anatomy depending on the location, progression, and severity of the symptoms. If the pain symptoms do not respond to NSAIDs and combined hormonal contraception, then a pelvic ultrasound is indicated. If medical management fails to control the symptoms and the pelvic ultrasound is normal, then laparoscopy is recommended for definitive diagnosis.

B Dysfunctional uterine bleeding (DUB) (see Chapter 23). DUB is defined as excessive, prolonged, or irregular bleeding not associated with an anatomic lesion. Most adolescent girls have anovulatory menstrual periods for the first 2 to 3 years following menarche. Approximately 2% of adolescents ovulate regularly in the first 6 months after menarche and 18% by the end of the first year, making DUB common in this age group.

1. **Etiology.** The cause of DUB in 75% of cases is an immature hypothalamic–pituitary axis, resulting in anovulation. Other causes include psychogenic factors, juvenile hypothyroidism, and coagulation disorders (von Willebrand disease).
2. **Clinical picture**
 - a. **Menometrorrhagia** (irregular, heavy bleeding) is the most characteristic symptom.
 - b. Bleeding can be prolonged and heavy, in some cases leading to severe anemia.
 - c. The condition is usually self-limited.
3. **Management.** Therapy involves the use of cyclic hormonal manipulation with progestins or combined oral contraceptive pills. Bleeding disorders must be ruled out in patients with heavy bleeding as up to 20% of teens with menorrhagia have some sort of bleeding problem.

C Amenorrhea (see Chapter 22). Primary amenorrhea is defined as no menstrual flow by 16 years of age, or within 2 years of breast development. Chromosomal abnormalities account for approximately 30% to 40% of all cases of primary amenorrhea. Secondary amenorrhea is menstruation that ceases for more than 6 months.

1. **Müllerian anomalies and vaginal agenesis** account for 20% of cases of primary amenorrhea. The incidence of renal or urinary tract anomalies in patients with müllerian anomalies is approximately 45%. Treatment is usually surgical.

- a. **Mayer–von Rokitansky–Küster–Hauser syndrome** involves vaginal agenesis with or without uterine agenesis. Adolescents may present with cyclic abdominal pain and amenorrhea when endometrial tissue is present within one or both of the uterine remnants (see Chapters 21 and 22).
- b. **Imperforate hymen** results in obstructed outflow of menstrual blood. Affected patients present with amenorrhea and cyclic abdominal pain. A bulging introitus and pelvic mass are present on examination. An imperforate hymen is not a true müllerian anomaly because the hymen is derived from the urogenital sinus. However, it is treated as a müllerian anomaly.
2. **Hypogonadotropic hypogonadism.** This condition is characterized by a deficiency of hypothalamic hormone secretion. It accounts for 40% to 50% of all cases of amenorrhea.
 - a. **Kallmann syndrome** is a rare autosomal dominant disorder that involves a deficiency of GnRH. It is associated with anosmia.
 - b. **Central nervous system lesions**, including craniopharyngioma and pituitary adenoma, may cause hypogonadotropic amenorrhea.
 - c. **Anorexia nervosa**, a condition characterized by extreme weight loss with no known organic cause, can affect adolescent development and result in amenorrhea. Psychiatric symptoms may be present, and occasionally the outcome is fatal.
 - d. **Female athlete triad** is a syndrome defined by amenorrhea, disordered eating, and osteoporosis. Typically, this condition is seen in athletes whose performance is enhanced by a lean physique, such as ballet dancers, ice skaters, and long-distance runners. The etiology most likely involves an inadequate caloric intake for the level of energy expended, which leads to hypoenvironment and amenorrhea.
3. **Gonadal dysgenesis** (hypergonadotropic hypogonadism). This condition is characterized by absence of secondary sex characteristics, infantile but normal genitalia, and streak-like gonads that are devoid of germ cells and appear as fibrous white streaks. The presence of a Y chromosome dictates early removal of the gonads because of their propensity for malignancy (25% of cases occur by the age of 15 years). The different forms of gonadal dysgenesis are as follows:
 - a. **Turner syndrome** (45,X) is characterized at birth by low weight, short stature, edema of the hands and feet, and loose skin folds on the neck. Adolescent patients have short stature, lack of sexual maturation, a low posterior hairline, prominent ears, a broad chest, widely spaced nipples, and epicanthal folds. Cardiac anomalies are common in these patients.
 - b. **Swyer syndrome** (46,XY) is characterized by a female phenotype with amenorrhea and lack of secondary sex characteristics. Growth is usually normal, and some virilization may occur after puberty, especially when gonadal tumors are present. Swyer syndrome is inherited as an X-linked recessive trait. The clinical picture without virilization and tumor propensity may also occur in 46,XX individuals. This condition is termed pure gonadal dysgenesis and is an autosomal recessive inheritance.
 - c. **Mixed gonadal dysgenesis** (45,X/46,XY mosaicism) is characterized by sexual ambiguity in newborns. Internal structures include müllerian and wolffian derivatives. Asymmetric development of the gonads is expressed as a testis or gonadal tumor on one side with a streak-like, rudimentary gonad, or no gonad on the other side.
 - d. **Abnormalities of the X chromosome** (e.g., mosaicism, isochromosome, short-arm X deletion, long-arm X deletion, and translocation) result in amenorrhea and varying degrees of Turner syndrome.
4. **Ovarian failure.** This condition, which is rare in adolescents, is usually attributed to genetic defects (e.g., Turner mosaic [45X/46XX], or deletion a portion of the long arm of the X chromosome), autoimmune conditions, radiation or chemotherapy for cancers, or galactosemia. Treatment involves estrogen and progesterone replacement.
5. **Polycystic ovary syndrome** (see Chapter 24). This condition is the **most common cause of anovulation** and secondary amenorrhea in the adolescent age group. This syndrome is characterized by oligomenorrhea, hirsutism, acne, and polycystic-appearing ovaries on ultrasound. The syndrome is associated with obesity (50% to 70%), insulin resistance, and the development of diabetes. Combined hormonal contraceptives are the mainstay of therapy for menstrual cycle regulation and control of hirsutism and acne. Antiandrogen agents are also beneficial, especially

in combination with combined hormonal contraceptives. In addition, weight loss effectively improves symptoms in obese individuals.

6. **Systemic illnesses.** Renal failure, diabetes mellitus, cystic fibrosis, and hemoglobinopathies (sickle cell anemia and thalassemia) may cause hypothalamic amenorrhea.
7. **Other endocrine gland disorders.** Thyroid disease, late-onset CAH, Cushing syndrome, and pituitary adenomas may all cause amenorrhea.

D Contraception Most sexually active adolescents do not use contraception, especially at the time of the first sexual act. Because younger patients probably do not mention contraception, a discussion about the use of contraceptives and preventing the transmission of sexually transmitted diseases should follow a physical examination, regardless of whether the patient is sexually active.

E Sexual abuse Defined as sexual touch by someone at least **5 years older than the adolescent**, sexual abuse incorporates a wide range of behavior, from coerced seduction to violent assault. Rape is a form of sexual abuse. Seven percent of American men and women between 18 and 22 years of age have experienced at least one episode of nonvoluntary sexual intercourse.

1. Lack of findings on examination does not mean that abuse did not occur. A thorough history, assessment of family and environment, and laboratory studies should accompany the examination to establish the diagnosis.
2. Follow-up studies suggest that many people, particularly adolescents, may remain psychologically impaired and even suffer from posttraumatic stress disorder long after the abuse has ended.



Study Questions for Chapter 20

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. An 11-year-old girl presents with a 1.5-month history of a persistent white colored vaginal discharge that is watery and odorless. There is no associated pain or pruritis. Examination reveals Tanner stage III breasts and stage II pubic hair. Wet mount is negative for clue cells and yeast. Please select the most appropriate management:

- ☐ A Remove the foreign body
- ☐ B Treat with a course of cefixime
- ☐ C Recommend application of Clotrimazole cream
- ☐ D Observation
- ☐ E Treat with a course of Mebendazole

2. A concerned mother brings her 17-year-old daughter to your office for a second opinion. The patient appears to have normal female secondary sexual characteristics with normal breast development as well as normal pubic and axillary hair growth. However, the mother is very concerned because her child still has not gotten her period. After review of the records you learn that the initial gynecologist made a diagnosis of a müllerian agenesis after obtaining an abnormal pelvic ultrasound and a normal (46,XX) karyotype. You recommend:

- ☐ A MRI of the brain to rule out any intracranial masses
- ☐ B MRI of both ovaries
- ☐ C Complete retroperitoneal ultrasound to evaluate for renal or urinary tract anomalies
- ☐ D Immediate removal of bilateral gonads due to risk of malignancy
- ☐ E Cyclic oral contraception

3. A 16-year-old girl had had irregular vaginal bleeding every 1 to 4 weeks since she first started menstruating approximately 10 months ago. The bleeding is usually light but sometimes is heavy. Her last episode of bleeding (moderate in quantity) lasted for about 2 weeks. The next best step is to:

- ☐ A Perform an endometrial biopsy
- ☐ B Start oral contraceptives
- ☐ C Placement of an intrauterine device
- ☐ D Obtain a pregnancy test
- ☐ E Obtain a pelvic ultrasound

4. A mother brings her 18-year-old daughter in to see you because she has not started to develop breasts and has not had a period. You diagnose delayed puberty. Which one of the following statements is true?

- ☐ A Constitutional delay of puberty is the most common cause of delayed puberty
- ☐ B Kallman syndrome is defined as hypergonadotropic hypogonadism due to isolated GnRH deficiency
- ☐ C Turner syndrome is associated with risk of gonadoblastoma so the gonads must be removed at time of diagnosis
- ☐ D Hypergonadotropic hypogonadism affects approximately 50% of patients presenting with delayed puberty
- ☐ E Radiation therapy to the ovaries is associated with delayed puberty due to hypogonadotropic hypogonadism

5. A pediatrician asks you to consult on a case of a baby that was born with because they are not able to assign a gender. There is a significant degree of clitoral enlargement and labial folds are uncharacteristically large and partially fused. You recommend:

- ☐ A Ultrasound to evaluate the internal reproductive organs
- ☐ B Karyotype
- ☐ C Serum sodium level
- ☐ D 17-OH-progesterone level
- ☐ E Tell the parents they have a baby girl

6. A 15-year-old female is brought to your office complaining of severe dysmenorrhea that has become progressively worse since the onset of menses. Menarche occurred at age 13. The pain is located predominantly on the right side, lasts for the duration of the menstrual flow, and at its worst is associated with nausea and vomiting. She has had to miss school with every menstrual period for the past year. She has tried nonsteroidal medications, which initially helped but no longer relieve the pain significantly. The next step in management is:

- ☐ A Take the maximal dose of nonsteroidal medications and see if pain is improved
- ☐ B Refer her to psychiatry since this may just be a ploy to get out of school
- ☐ C Start combined oral contraceptive hormone pills
- ☐ D Obtain a pelvic ultrasound
- ☐ E Perform a laparoscopy to evaluate for endometriosis

7. An 8-year-old girl is brought to your office by her mother because of occasionally bloody vaginal discharge. Her mother suspects sexual abuse because she does not “know of any other reason why a little girl should be bleeding from her vagina.” She has no other medical history except for a throat infection a few weeks ago, which was treated with penicillin. On physical examination, she has enlargement of both breasts and enlarged areolae. There is no axillary hair growth. No pubic hair is apparent. The external genitalia have an age-appropriate clitoris and normal labia minora. There are no bruises, hematomas, or lacerations. You take a culture of the vaginal discharge, which is pink to red colored and not foul smelling. You are not able to perform a more thorough examination. The most likely cause of her vaginal bleeding is:

- ☐ A Precocious puberty
- ☐ B Sexual abuse
- ☐ C Foreign body
- ☐ D Bacterial infection
- ☐ E Pinworm

8. A 6-year-old girl is brought to your office because she has had four urinary tract infections within the last 3 months. While the mother is holding her, you examine her genitalia. There is lack of pubic hair. The labia minora are in apposition but are easily separable with gentle traction. You note a 1-cm-sized clitoris. There is a 0.3-cm cystic structure in the inferior aspect of the urethra, which is nontender to cotton swab palpation; however, it has left a red hue on your cotton swab. You order a urinalysis and a urine culture and sensitivity. The safest and next best step in management is:

- ☐ A Estrogen cream
- ☐ B Sitz baths
- ☐ C Intravenous pyelography
- ☐ D Low-potency steroid cream
- ☐ E Surgical repair

9. You are a world-renowned reproductive endocrinologist and are asked to make a diagnosis for a patient who has ambiguous genitalia. Here are the data:

Karyotype	XY
Spermatogenesis	Absent
Müllerian structures	Absent
Wolffian structures	Present
External genitalia	Male hypospadias
Breast	Gynecomastia

The diagnosis is:

- ☐ A True hermaphroditism
- ☐ B Mixed gonadal dysgenesis
- ☐ C Swyer syndrome
- ☐ D Complete androgen insensitivity
- ☐ E Reifenstein syndrome



Answers and Explanations

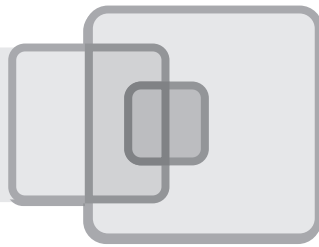
1. **The answer is D** [II E]. The discharge described is consistent with normal physiologic discharge secondary to estrogen stimulation. There are no signs or symptoms of a foreign body. There is no need to treat with Cefixime which is indicated to treat vulvovaginitis associated with organisms susceptible to cephalosporins such as *Shigella*. *Shigella* is associated with a persistent and odorless vaginal discharge but it is bloody and often associated with recent bout of diarrhea and ingestion of contaminated food or water. Clotrimazole is an antifungal that can be applied topically for candidal infections. This patient does not exhibit symptoms or evidence of such an infection. A single dose of mebendazole is used for pinworms (*Enterobius vermicularis*) which present with symptoms of vulvar and perianal pruritis. This patient does not exhibit these symptoms.
2. **The answer is C** [IV A]. Primary amenorrhea is defined as no menstrual blood flow by 16 years of age or within 2 years of breast development. Since this girl has not reached menarche by the age of 17 years, an evaluation is warranted, and a diagnosis of müllerian agenesis has been made by her gynecologist. Müllerian agenesis is estimated to account for 20% of primary amenorrhea. The incidence of renal or urinary tract anomalies in patients with müllerian anomalies is approximately 45%. Therefore, the patient should be evaluated for renal or urinary tract anomalies. MRI of both ovaries or pelvic ultrasound will not add any additional information to the recently obtained abnormal pelvic ultrasound. There is no indication to remove both ovaries in this female (XX) patient. If the patient instead had minimal to absent secondary sex characteristics, streak-like gonads and the presence of a Y chromosome, then removal of the gonads would be indicated. In such scenarios, 25% of malignancies develop by the age of 15 years.
3. **The answer is D** [VII B]. Abnormal uterine bleeding is due to either a structural lesion or a hormonal imbalance. In adolescents, the most common cause for abnormal uterine bleeding is anovulation and pregnancy. Obtaining a pregnancy test is always the first step in the evaluation and management of abnormal bleeding for reproductive age women. Although it is likely that this patient has anovulatory or oligovulatory bleeding and using oral contraceptives may be important for treatment, it is most important to first rule out pregnancy.
4. **The answer is D** [VI D]. Hypergonadotropic hypogonadism is the most common cause of delayed puberty and affects approximately 50% of girls presenting with delay of puberty. Constitutional delay accounts for only 10% to 20% of cases. Kallman syndrome is caused by failure of migration of GnRH neurons and leads to hypogonadotropic hypogonadism as there is no production of GnRH from the hypothalamus and therefore no secretion of gonadotropins or estrogen. Turner syndrome is not associated with risk of gonadoblastoma, only if a Y chromosome fragment is present. Radiation to the ovaries is associated with ovarian failure and hypergonadotropic hypogonadism.
5. **The answer is C** [V A 2]. CAH caused by the 21-hydroxylase defect is the most common cause of distinct virilization of the female newborn. Its incidence is 1 in 5,000 births and accounts for 95% of all cases of CAH. The chromosomes, gonads, and internal genitalia are female but the external genitalia are virilized to varying degrees due to excess production of fetal androgens during development. Although it is important to confirm the diagnosis with a serum 17-OH-progesterone level, the most crucial first step is to evaluate serum electrolytes because salt wasting may be present and can be fatal in the neonatal period. Repletion of necessary electrolytes is critical as is suppression of the adrenal gland. A karyotype should be obtained later to rule out other causes of ambiguous genitalia, such as hermaphroditism and mixed gonadal dysgenesis. You should not assign a gender until you have all of the information.
6. **The answer is D** [VII A 1 to 3]. The significant factors in this patient's history are the progression of her symptoms, the severity, and the localized nature of the pain. Primary dysmenorrhea may be severe, but is usually diffuse throughout the pelvis and does not become progressively worse over time. The history in this patient suggests secondary dysmenorrhea, possibly an obstructive müllerian anomaly. For this reason the next step should be a pelvic ultrasound. Combined hormonal contraceptives

would be the next step if the pain did not localize and there was no significant progression of pain symptoms with each menses. She is already on NSAIDs, so increasing the amount would not be beneficial given the severity of the symptoms. A laparoscopy would not be appropriate at this point without first performing an ultrasound and maximizing medical therapy. Although sometimes pelvic pain can be attributed to psychiatric causes, it is rare, and the patient should have all structural abnormalities investigated and optimal medical therapy tried first.

7. The answer is D [II E 1 b 2]. Given the clinical scenario, the only cause that is consistent is hemolytic streptococcal throat infection that has translated into vaginitis weeks later. Although sexual abuse should always be suspected with bloody vaginal discharge, the evidence is lacking, and the mother has no good reason to believe that her daughter has been sexually abused. Precocious puberty is unlikely in an 8-year-old girl with isolated development of the breast (thelarche) without pubarche. Pinworm would present with intense vaginal and perianal itching, especially at night. Given her older age and lack of information in the clinical scenario (especially because the discharge is not foul smelling), foreign body is less likely.

8. The answer is B [II D 2 a]. The diagnosis is prolapsed urethra, characterized by a small, hemorrhagic, friable (blood on cotton swab), painless mass surrounding the urethra. The safest and least expensive initial therapy is sitz baths. The bathtub is filled with lukewarm water with or without Epsom salt, and the patient sits in the bathtub a few times each day. Estrogen cream would be the next step in treatment. Intravenous pyelography would be useful if the diagnosis were ectopic ureter. Low-potency steroid creams are useful for lichen sclerosus. Surgical repair of prolapsed urethra is not necessary unless the patient has urinary retention or necrosis is present.

9. The answer is E [V E 1 e]. The two most important syndromes that have an XY karyotype are the AIS (complete, Reifenstein [incomplete], 5- α -reductase) and Swyer syndrome. Complete androgen insensitivity syndrome (CAIS) has the following features: XY, no spermatogenesis, absent müllerian structures, absent wolffian structures, *female external genitalia*, and female breast development. Reifenstein syndrome is exactly the same as CAIS except for more “male influence”: wolffian structures are present, external genitalia are male (male hypospadias), and breasts are not as well developed (gynecomastia). Swyer syndrome is different from AIS in that there is more of a “female influence.” This syndrome is characterized by the *presence of müllerian structures*, *absence of wolffian structures*, infantile female external genitalia, and lack of breast development. Mixed gonadal dysgenesis is characterized by mosaicism for 45,X/46,XY. There is usually a streak gonad on one side and a functioning testis on the other side. Both wolffian and müllerian structures are present and the external genitalia are ambiguous (although a wide range of phenotypes is possible). A true hermaphrodite has both testicular tissue (XY genotype plus testicular tissue histology) and ovarian tissue (XX genotype plus ovarian tissue histology). One gonad can be a testis and the other an ovary, or one gonad can have both tissue types (“ovotestis”). True hermaphrodites have ambiguous external genitalia, which are most often more in the male spectrum than in the female. They also have gynecomastia.



Müllerian Anomalies and Disorders of Sexual Development

LAUREN W. MILMAN • SAMANTHA M. PFEIFER

I

INTRODUCTION

A **Müllerian anomalies** is the broad term used to group together several specific structural abnormalities resulting from abnormal embryological development of the uterus, cervix, fallopian tubes, or vagina. Normal development of these organs requires coordinated cellular development, replication, migration, fusion, and regression which are influenced by the presence or absence of certain genetic, epigenetic, and hormonal elements. Women with these abnormalities can have a wide range of clinical manifestations. They can be asymptomatic, or present with primary amenorrhea, infertility, recurrent miscarriages, or preterm delivery.

B **Epidemiology**

1. In the general population, the prevalence of anomalies has been reported to be anywhere between 0.17% and 6.7%.
2. Given that müllerian anomalies can cause infertility and miscarriage, the prevalence is higher in these populations, ranging from 3% to 10%.

II

EMBRYOLOGIC DEVELOPMENT OF THE FEMALE GENITAL TRACT

A **Sex determination**

1. Fertilization is the point at which genetic and chromosomal sex is determined on the basis of whether the sperm is X- or Y-bearing, resulting in XX or XY sex chromosomes.
2. The **SRY gene** on the short-arm of the Y chromosome encodes for the testes-determining factor, which is necessary for normal development of the **mesonephric (wolffian) duct** system, including the testes. The androgen, testosterone, and dihydrotestosterone, made by the fetal testes, are needed for development of the male phenotype.
3. Absence of the Y chromosome, and thus, the SRY gene, as seen in the XX chromosome complex, allows for female sex differentiation. Development of the female phenotype is not under fetal hormonal influence.
4. The **antimüllerian hormone**, produced by the Sertoli cells of the fetal testes is necessary to inhibit development of the **paramesonephric (müllerian) duct** system seen in normal females.
5. The **WNT4 gene** on chromosome 1 has been shown to encode for a protein which is involved in müllerian duct formation, androgen production, and oocyte development and development of the kidneys.

B **Müllerian duct and urogenital sinus development**

1. After approximately 6 weeks of embryologic development, the müllerian and wolffian duct systems become distinguishable from one another.

- a. Absence of the antimüllerian hormone allows for the müllerian ducts to develop on the lateral surface of the mesonephros, arising from the **mesoderm**.
 - (1) The superior portions develop into the fallopian tubes bilaterally.
 - (2) The posterior portions develop and fuse in the midline (10 weeks of gestation) to form a Y-shaped structure that will become the uterus, cervix, and superior vagina.
 - (3) The lateral fusion results in a thick septum that usually reabsorbs between 13 and 20 weeks' gestation.
- b. The **urogenital sinus** is derived from the **endodermal layer** and gives rise to the mid and inferior portions of the vagina.
 - (1) The sinovaginal bulbs fuse to form the vaginal plate
 - (2) The central cells of the vaginal plate regress to form the lumen of the vagina
 - (3) The hymen develops from the invagination of cells along the posterior wall of the urogenital sinus. This tissue separates the vaginal lumen from the cavity of the urogenital sinus
 - (4) Canalization of the lower vagina usually occurs between 20 and 22 weeks of gestation.
- c. Development of certain portions of the renal system and axial skeleton are linked temporally and spatially to the development of the reproductive system. Thus, structural abnormalities of the reproductive system can be associated with abnormalities of these other organ systems.

III

TYPES OF DEFECTS OF MÜLLERIAN DEVELOPMENT AND CLINICAL PRESENTATION

Defects in development of müllerian structures can be classified as lateral fusion defects or vertical fusion defects. However, it is important to remember that developmental defects can be variable and do not necessarily fall into distinct categories.

- A** **Lateral fusion defects** usually results from varying degrees of lack of fusion of portions of the uterus and cervix, or lack of regression of cell layers at the site of fusion (Fig. 21–1).

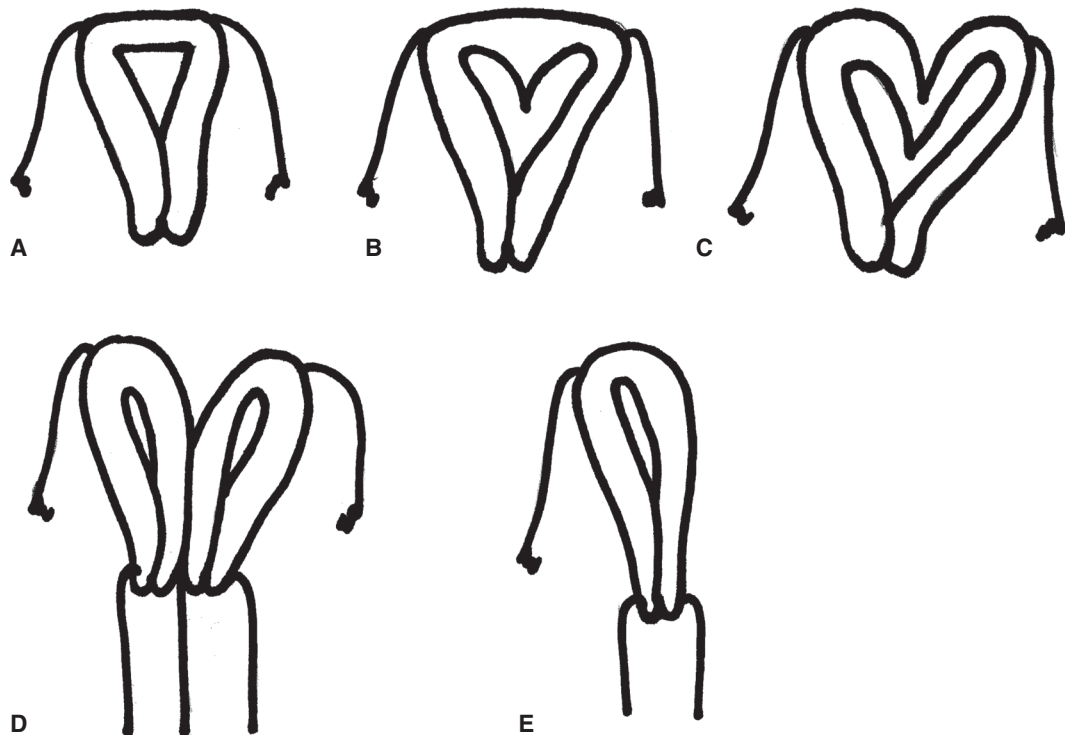


FIGURE 21–1 Image depicting the uterine anomalies attributed to lateral fusion defects. **A.** Normal uterus with clear triangular endometrial cavity depicted. **B.** Septate uterus with single cervix. Note the fundal contour is smooth, but the cavity is “heart shaped.” **C.** Bicornuate uterus with single cervix. Both the outer uterine contour and the endometrial cavity are “heart shaped.” **D.** Uterus didelphys with complete longitudinal septum. The uterine cavities are completely separate but adjacent. **E.** Unicornuate uterus. The other side failed to form.

1. **Septate uterus** comprises approximately 50% of all müllerian anomalies. After the fusion of the paramesonephric ducts, a septate uterus forms if there is partial failure of resorption of the uterovaginal septum. This anomaly is distinguished from bicornuate uterus by a single fundus. Like bicornuate uterus it most commonly has a single cervix, but may be associated with a duplicated cervix and longitudinal vaginal septum.
 - a. **Clinical presentation**
 - (1) This anomaly has a marked association with early pregnancy loss, or recurrent spontaneous abortion, mid-trimester loss, and preterm birth. Prevalence is noted anywhere from 25% to 85%.
 - b. **Diagnosis** usually made with hysterosalpingogram, 3D ultrasound (US), or on hysteroscopy. Differentiation from bicornuate uterus is made by 3D US, MRI, or laparoscopy to evaluate the uterine fundus. Associated with renal anomalies.
 - c. **Management** usually involves hysteroscopic resection of the septum.
2. **Bicornuate uterus** is considered to be the second most common müllerian anomaly, with approximately 10% prevalence. It is the result of incomplete fusion of the uterovaginal horns. This anomaly can have a single cervix or duplicated cervix.
 - a. **Clinical presentation** can include late second-trimester preterm birth, recurrent spontaneous abortion, mid-trimester loss or can be asymptomatic. Associated with renal anomalies.
 - b. **Diagnosis** usually made with hysterosalpingogram, 3D US, and MRI which shows two uterine bodies and a single cervix.
 - c. **Management** involves careful obstetrical management of the pregnancy. Surgical techniques to unify the uterine horns are reserved for repeated obstetric losses despite careful obstetrical care. These procedures involve laparotomy with opening and combining the two horns (Strassman or modified Tompkins metroplasty) and are rarely performed.
3. **Unicornuate uterus** can account for up to 20% of müllerian anomalies and occurs when there is failure of one paramesonephric duct to develop. One-third of cases can be isolated, while two-thirds are generally associated with a rudimentary uterine horn, half of which can have active endometrial tissue.
 - a. **Clinical presentation** includes spontaneous abortion and preterm labor and birth, intrauterine growth restriction, malpresentation of the fetus likely secondary to the overall reduction in uterine muscle mass.
 - (1) This anomaly can also be associated with a residual blind uterine horn on the other side. If there is active endometrium within this blind horn, it can lead to worsening dysmenorrhea as there is no outlet for the cyclic shedding of the endometrial lining.
 - (2) Almost half of women with these anomalies can have **associated urologic anomalies**, including ipsilateral renal agenesis, horseshoe kidney, or ipsilateral pelvic kidney.
 - b. **Diagnosis** is usually made after the presentation including pelvic pain, and dysmenorrhea with the associated hematometra or endometriosis. Hysterosalpingogram can be useful in diagnosis of a unicornuate uterus as there will only be one fallopian tube coming from the uterus. Ultrasound is recommended as screening test for renal anomalies. If a blind uterine horn is suspected in addition to the unicornuate horn, then MRI is recommended.
 - c. **Management** for pregnancy is primarily proactive obstetrical care to monitor for preterm labor and delivery. These women should not carry twin pregnancy, and therefore care should be taken with fertility drugs. Single embryo transfer is recommended for in-vitro fertilization (IVF). When a blind horn is present, surgery usually consists of the laparoscopic resection of the rudimentary horn.
4. **Uterine didelphys** accounts for approximately 5% of müllerian anomalies and results from virtually complete failure of fusion of the paramesonephric ducts. In these cases, each duct essentially develops into a separate hemiuterus, each with its own fallopian tube and cervix. It is usually associated with a longitudinal vaginal septum that can be minimal or extend to the introitus.
 - a. **Clinical manifestation.** Women with this class of anomalies are usually asymptomatic. However, they may present with dyspareunia due to the longitudinal septum. They will also present complaining that tampons “do not work” as the tampon only effectively absorbs menstrual flow from one hemivagina. **Unilateral renal agenesis** is most commonly associated with this anomaly, with a reported incidence of up to 20%. Pregnancies can occur in either cavity, and

can be associated with pregnancy loss, preterm birth, and occasionally have been reported to occur simultaneously in both cavities, as dizygotic twins. There can also be a long interval between births of each twin, ranging in case reports from 5 days to 8 weeks. Delivery is often by cesarean section due to malpresentation, but vaginal births can occur.

- b. **Diagnosis** usually occurs after menarche, with the complaint that tampon use does not obstruct menstrual flow or dyspareunia. Many women are asymptomatic and are diagnosed at time of first pelvic examination. On initial pelvic examination, two vaginal canals and two cervixes can be identified. Diagnosis is usually made by clinical examination, with ultrasound confirmation of two separate horns, or MRI. Renal ultrasound is advised to screen for renal anomalies.
- c. **Management** for obstetrical care is expectant. There is no need for surgical intervention to correct the anomaly prior to pregnancy.

B Lateral fusion defects associated with obstruction (Fig. 21–2)

1. **Bicornuate/septate uterus with obstructed uterine horn.** One of the hemiuterine cavities does not communicate with the other side or a cervix leading to build up of menstrual flow within the obstructed hemiuterus. Incidence is rare.
 - a. **Symptoms.** These patients usually present during adolescence shortly after menarche with cyclic dysmenorrhea or pain that is progressive and often unilateral, reflecting one obstructed side. If the diagnosis is delayed, these patients can present with a pelvic mass with compression symptoms. The pain associated with this anomaly is often due to pressure from the obstructed side, but endometriosis can develop from retrograde menstruation from the obstructed side causing pain symptoms. This anomaly is associated with ipsilateral renal agenesis.
 - b. **Diagnosis** is often delayed as a müllerian anomaly is not considered in the differential as the patient is having regular menstruation. The diagnosis is by ultrasound with MRI to determine the exact location of the obstruction. A müllerian anomaly must be considered in any female with a known history of congenital renal agenesis.

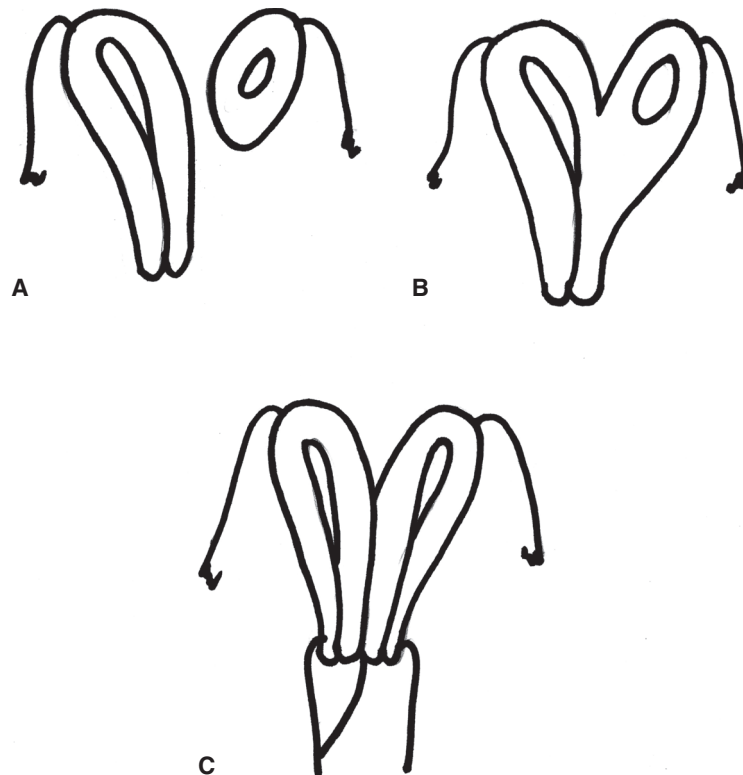


FIGURE 21–2 Image depicting lateral fusion defects with obstruction. **A.** Unicornuate uterus with separate blind uterine horn with functional endometrium within. **B.** Bicornuate uterus with obstructed noncommunicating horn that is part of the uterus. **C.** Uterus didelphys with obstructed hemi-vagina.

- c. **Treatment** involves resection of the blind obstructed uterine horn with careful reconstruction of the remaining hemiuterus. Unifying the obstructed and nonobstructed horns is feasible only if the septum separating the cavities is very thin. The remaining hemiuterus will function well for pregnancy, though careful obstetrical care is needed.
2. **Double uterus, blind hemivagina, and ipsilateral renal agenesis** results from damage to caudal portion of the mesonephric duct. The right side is obstructed 66% of cases. Ipsilateral renal agenesis is more frequently associated with a right-sided obstructed hemivagina.
 - a. **Symptoms** include severe dysmenorrhea, unilateral pelvic pain, chronic pelvic pain, and paravaginal mass. Menstruation occurs normally and may lead to symptoms being attributed to cause other than gynecologic.
 - b. **Diagnosis** is often delayed as a müllerian anomaly is not considered. Adolescents who have a history a congenital renal agenesis and present with pelvic pain or dysmenorrhea must be considered to have a müllerian anomaly as the cause of their pain. Ultrasound is a valuable and easy screening test, but MRI is gold standard for determining the exact anatomy.
 - c. **Treatment** involves resecting the blind vaginal septum. Accumulated menstrual blood will evacuate and the anatomy will be restored to normal. It is not necessary to perform laparoscopy unless there is evidence of ovarian cysts or hematosalpinges (menstrual blood accumulated in fallopian tubes). Fertility depends on early diagnosis, but is essentially normal.

C Vertical fusion defects These anomalies are usually associated with an obstruction to the menstrual outflow and therefore present at puberty with pain and amenorrhea (Fig. 21–3). Since menstruation cannot occur, these adolescents may have a delay in diagnosis as a gynecologic cause for their symptoms may not be considered as they have not yet experienced “menarche.”

1. **Imperforate hymen** occurs when the central portion of the hymen, or fibrous connective tissue at vaginal introitus, does not regress. This results in obstruction of the vaginal canal. This is not a true müllerian anomaly, as it represents failure of degeneration of cells of urogenital sinus. Incidence is 0.1%.

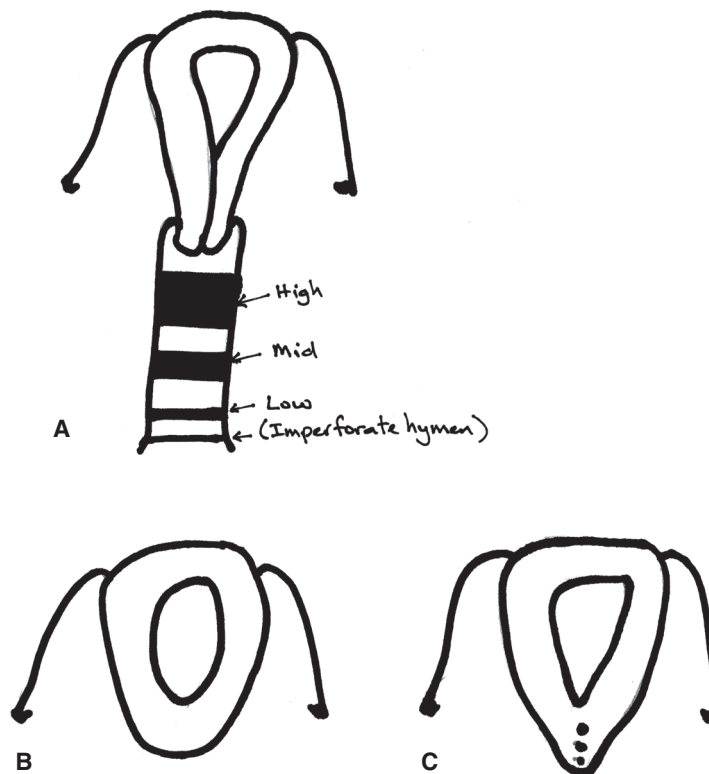


FIGURE 21–3 Image depicting vertical fusion defects. **A.** Transverse vaginal septum. Note the high transverse vaginal septum is thick, and can encompass the whole distance down to the introitus. The low transverse vaginal septum is usually thinner and can mimic an imperforate hymen. **B.** Cervical agenesis. **C.** Cervical dysgenesis. Note cervical “tissue” with isolated glands within.

- a. **Clinical manifestations.** Patients can present with cyclic sporadic, or chronic pelvic pain and hematocolpos. The episodes of pain correspond to menstruation, but since no menstrual flow occurs, these pain symptoms are often attributed to other causes leading to a delay in diagnosis. If the hematocolpos is large, it can cause urinary retention, which can be the presenting symptom. A large hematocolpos can cause abdominal distention from the mass effect.
 - b. **Diagnosis** can be made on physical examination showing an abdominal/pelvic mass extending from the symphysis to the umbilicus. Examination of the genitalia reveals a blind vagina with a bulging introitus on valsalva that may have a bluish hue due to the hematocolpos. Imaging with ultrasound or MRI is recommended to confirm the diagnosis as imperforate hymen, transverse vaginal septum, and cervical agenesis can have similar presentations and physical findings.
 - c. **Management** involves resecting the hymenal tissue to maintain patency. Fertility is normal and delivery can be vaginal.
2. **Transverse vaginal septum** is formed when tissue between the caudal area of the fused müllerian ducts and the vaginal plate does not resorb. This results in an upper vagina and a lower vagina separated by a septum. The septum can be high in the vagina or low towards the introitus. Lower transverse septum is usually thin and can be confused with imperforate hymen. Upper transverse vaginal septum is usually thick and must be distinguished from cervical agenesis. This anomaly is very rare but can be associated with other defects including on imperforate anus, coarctation of the aorta, atrial septal defect, bicornuate uterus, and lumbar spine malformations. The septum can also have a microperforation allowing egress of menstrual blood and presents as a shortened vagina with no visible cervix.
 - a. **Clinical manifestations.** Transverse vaginal septum presents as cyclic, sporadic, or chronic pelvic pain in the absence of menstruation (i.e., primary amenorrhea). Physical examination can reveal a palpable pelvic mass if the obstruction is low in the vagina and there is a large hematocolpos, but genital examination does not usually reveal any bulge at the introitus as the obstruction is usually higher.
 - b. **Diagnosis** is often delayed as pain symptoms in absence of menarche are usually attributed to causes other than gynecologic. Ultrasound is a useful screening test, but MRI is recommended to determine the exact location of the obstruction to better plan surgical treatment and distinguish from cervical agenesis.
 - c. **Management** involves surgical excision of the septum by vaginal approach, with anastomosis of upper and lower vaginal canals. A z-plasty technique is favored to avoid an annular stricture at the anastomosis site, and postoperative dilators are used to decrease stricture formation.
3. **Cervical agenesis/hypoplasia.** Complete cervical agenesis can occur with a normal vagina or in conjunction with complete vaginal agenesis.
 - a. **Clinical manifestations** include typically a presentation at the age of menarche with primary amenorrhea, and cyclic or even chronic pelvic pain. Development of pain is sooner to menarche than seen with transverse vaginal septum or imperforate hymen. Retrograde menstruation and development of endometriosis is common.
 - b. **Diagnosis** is usually made with ultrasound and MRI is necessary to differentiate this anomaly from transverse vaginal septum.
 - c. **Management** has traditionally involved removal of uterus as attempts to preserve the uterus and fertility by creating a fistulous tract between the vagina and the uterus have been complicated by multiple surgeries to maintain patency of the connection, infection, and even death. Recently, however, surgical anastomosis of the vagina to the uterus has been performed with some success in selected individuals to preserve fertility.
4. **Müllerian agenesis (Mayer–Rokitansky–Kuster–Hauser syndrome [MRKH])** as the name suggests, occurs with the lack of development of müllerian ducts.

The exact cause of this anomaly is unknown, but candidate genes include WNT4 and Hox mutations. The incidence is 1/4,000 to 5,000 births.

 - a. **Symptoms.** Patients present with primary amenorrhea. Ovarian function and pubertal function is normal, so breast development, pubic and function, axillary/pubertal hair, and pubertal

growth is unaffected. There is an absent or hypoplastic vagina and absent or abnormal müllerian structures. Approximately 7% to 10% have a rudimentary uterus that is high up in the pelvis. If there is functional endometrium within the remnant uterus, then the patient will have cyclic or chronic pain.

- b. Associated anomalies. MRKH is associated with renal anomalies in 36% of patients, 19% are severe such as renal agenesis, horseshoe kidney, etc. Skeletal anomalies are present in 28% of individuals.
- c. Karyotype is normal female: 46XX. This condition must be differentiated from complete androgen insensitivity syndrome (CAIS) (see below).
- d. **Diagnosis** is made by clinical examination showing normal breast, pubic and axillary hair development, and blind vagina. Imaging with ultrasound or MRI to confirm absence of uterus is recommended. A karyotype and normal testosterone levels distinguishes from CAIS.
- e. Treatment involves the following:
 - (1) Counseling. Many of these young females feel they are not “normal” and counseling can help overcome feelings of inadequacy.
 - (2) Creation of a neovagina for sexual function. This can be accomplished by nonsurgical dilation techniques which is the preferred method. Surgical options include McIndoe technique using skin graft placed in a surgically created space between the bladder and rectum, Vecchietti procedure, or the Davidoff procedure. Creating a neovagina using a portion of sigmoid colon is less commonly recommended.
 - (3) Fertility. A woman with MRKH can have a biologic child using her own oocytes through assisted reproductive technology and using a surrogate to carry the pregnancy.

IV

OTHER DISORDERS OF SEXUAL DEVELOPMENT

A CAIS results from loss of function mutation of the androgen receptors in 46XY genotype individuals. As the body does not respond to androgens, these individuals are phenotypically female, but lack internal female reproductive structures. This syndrome was previously referred to as “testicular feminization.”

1. **Clinical manifestation.** These females often present with primary amenorrhea at puberty. Examination reveals normal appearing external female genitalia, blind vagina, and absence or sparsity of pubic and axillary hair. The gonads are testes, and serum testosterone levels are in the male range. Breast development is normal, as the androgens produced by the testes are aromatized to estrogens leading to breast development. The presentation can also be during childhood with testes present within inguinal hernias. These individuals must be distinguished from MRKH as the presence of a Y chromosome places these individuals at risk for malignant transformation of the gonad and gonadectomy is recommended.
2. **Diagnosis** of CAIS is made by physical examination, imaging confirming absence of internal female reproductive organs, serum testosterone, and karyotype of 46XY. The diagnosis should be considered in any young female presenting with inguinal hernia or labial mass.
3. **Management** includes the following:
 - a. Counseling for the patient and family to understand and manage the issues surrounding disorders of sexual development (DSD). National support groups are available for individuals and families.
 - b. Creation of a neovagina. The approach is similar as for MRKH, with a nonsurgical technique favored.
 - c. Removal of the gonads. Unlike other conditions with presence of a Y chromosome, with CAIS gonadectomy is usually recommended after puberty to allow normal growth since development of gonadoblastoma is rare prior to puberty. Some are advocating leaving the gonads in place and monitoring for development of gonadoblastoma, but this is not standard.
 - d. Hormonal support with estrogen in absence of gonads. Dosage is higher than for a postmenopausal woman to promote bone growth and secondary sexual characteristics.
 - e. Fertility treatment is not possible as there are no oocytes, nor a uterus to carry a pregnancy. Adoption is the only option.

B Partial androgen insensitivity syndrome (PAIS) is the category for several different phenotypes, all with some variation of mutation of androgen receptors.

1. **Clinical manifestations** vary widely. The female phenotype is similar to the patient with complete androgen insensitivity, but generally exhibits differing degrees of ambiguous genitalia axillary/pubertic hair at puberty. These individuals are usually raised female. The male phenotype, exhibited in **Reifenstein syndrome**, is infertile and typically includes hypospadias and bifid scrotum. There is also a range of external genitalia from microphallus with a normal urethra, to the creation of a pseudovagina and lack of scrotal fusion. These males typically have gynecomastia and normal pubic and axillary hair but no chest or facial hair.
2. **Diagnosis** can be challenging given the range of phenotypes. Karyotype is 46XY.
3. **Management** strategies are similar to those described with complete insensitivity. However, some surgical procedure is often performed to modify the ambiguous genitalia to facilitate gender assignment. This is an area that is still evolving.

C XY Gonadal dysgenesis is also known as **Swyer syndrome**. This typically occurs when there are mutations of the SRY gene. In the presence of this defective gene, gonads do not differentiate into testes, and no testosterone or antimüllerian hormone is produced. Therefore, the development of the external genitalia in female müllerian ducts is not inhibited (no AMH) and normal female internal organs form. Gonads are nonfunctioning.

1. **Clinical manifestations** include an externally female appearance, with nonfunctioning gonads. Therefore, girls often present with delayed puberty, both lack of menstruation and failure of secondary sex characteristics development, such as breast development. The adrenal glands are unaffected, which allows for some androgen production. This results in the development of small amounts of pubic and axillary hair.
2. **Diagnosis** can be suspected in the setting of delayed puberty, with elevation in measured gonadotropins. This suggests that the pituitary is functioning normally, but the gonads are not responding. A karyotype is recommended, which reveals normal 46XY chromosomes. Pelvic ultrasound or MRI confirms the presence of a uterus, but no ovaries. This must be differentiated from 46XX gonadal dysgenesis and 45X (Turner syndrome).
3. **Management** involves the following:
 - a. Counseling for the patient and family to manage and understand the issues surrounding DSD.
 - b. Removal of gonads at the time of diagnosis, unlike CAIS.
 - c. Hormonal supplementation for initiation of puberty with estrogen alone, followed by addition of progesterone to facilitate regular menstruation as uterus is present.
 - d. Fertility is possible using assisted reproductive technology, and donor oocytes. The uterus in women with Swyer syndrome should be able to carry a pregnancy.

D Congenital adrenal hyperplasia (CAH) is characterized by multiple autosomal recessive diseases with varying mutations in the pathway of steroidogenesis in the adrenal glands. The majority of cases result from **21-hydroxylase deficiency**.

1. **Clinical manifestations:**
 - a. **Classic form** presents at birth with ambiguous genitalia and salt wasting.
 - b. **Nonclassic adrenal hyperplasia (NCAH)** is not associated with ambiguous genitalia. Presentation is in adolescence or adulthood with hirsutism, irregular menstruation, or infertility. It must be differentiated from PCOS.
2. **Diagnosis** is made by measuring 17-hydroxyprogesterone which will be elevated due to the 21-hydroxylase deficiency. Neonates with ambiguous genitalia must have serum electrolytes monitored for evidence of salt wasting, which can be life-threatening, and a karyotype.
3. **Management** for classic CAH includes replacement of adrenal steroids and surgical modification of external genitalia. These individuals are genetically female and are raised as female.

E 5-Alpha reductase deficiency is a disease in which the 5-alpha reductase enzyme is not present, and testosterone is not converted to dihydrotestosterone in peripheral tissues. Dihydrotestosterone is required in utero for normal development of male external genitalia. This disease is only seen in

those with a Y chromosome. There is normal production of antimüllerian hormone, and therefore no development of müllerian duct structures occurs. The result is ambiguous genitalia.

1. **Clinical manifestations** range from the appearance of normal male external genitalia, normal female genitalia, or ambiguous genitalia. These infants are born with testes and wolffian duct structures, but can have the appearance of female primary sex characteristics. These individuals can produce viable sperm. At puberty, these individuals can present with primary amenorrhea and may also have increased virilization, with testicular descent, and normal male-pattern hirsutism.
2. **Diagnosis** is considered with the presentation of the above-mentioned constellation of clinical manifestations. Absence of 5- α reductase is identified. There is usually a low or low-normal testosterone level, decreased levels of dihydrotestosterone, and a higher testosterone/dihydrotestosterone ratio.
3. **Management** mainly involves thoughtful gender assignment. Most are assigned to the female gender at birth. This population undergoes removal of testes and appropriate hormone replacement. Those assigned to the male gender can be given exogenous dihydrotestosterone before puberty to increase the size of the penis. Psychological support is also important given the difficulties that can occur with specific gender identity.

F **XX Gonadal dysgenesis**, as the name suggests, is hypogonadism in genetically female patients.

1. **Clinical manifestations.** These patients present with delayed puberty and normal female phenotype. The streak ovaries do not allow for normal estrogen and androgen production. Therefore, most secondary sex characteristics do not develop. Sparse pubic hair forms secondary to adrenal androgen production. These individuals do not have the phenotypic appearance of Turner syndrome.
2. **Diagnosis** is suspected when an otherwise-normal appearing female presents with delayed puberty, presence of pubic hair, and elevated levels of gonadotropins such as FSH and LH. A karyotype reveals normal XX chromosomes and imaging with ultrasound or MRI confirms the presence of a uterus, but no ovaries. This must be differentiated from 46XY gonadal dysgenesis as the gonads do not need to be removed as there is no Y chromosome.
3. **Management** involves:
 - a. Estrogen replacement to promote puberty and breast development with subsequent addition of progestin to regulate menstruation.
 - b. Estrogen dosing should be higher than postmenopausal woman to promote bone growth and secondary sexual characteristics.
 - c. The gonads do not need to be removed as there is no Y chromosome present.
 - d. Pregnancy can be achieved with assisted reproductive technology and donor oocytes.

G **Mixed gonadal dysgenesis** is most often diagnosed in the setting of a mosaic genotype: 45XO/46XY. There is typically a unilateral intra-abdominal testis, a streak gonad on the opposite side, and presence of müllerian structures. There is also a high risk of developing a gonadoblastoma, and as a result, removal of the gonads is recommended.



Study Questions for Chapter 21

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A 17-year-old female presents to you complaining of never having had a period. She reports breast development at the age of 13 years. She is 5'5" and weighs 125 lb. You suspect she has MRKH and not CAIS. Which one of the following is consistent with the diagnosis of MRKH but not with CAIS?

- ☐ A Elevated serum testosterone
- ☐ B Vaginal agenesis, absent uterus
- ☐ C Scant/absent pubic hair, normal axillary hair
- ☐ D Gonads should be removed
- ☐ E Pregnancy possible with gestational carrier

2. A 15-year-old female is referred to you because of worsening dysmenorrhea, associated with nausea and vomiting. She has had such severe vomiting that she has not been able to go to school for the past 6 months and has forced out of the cheerleading squad because of her frequent absences. The rest of her medical history is notable for asthma, irritable bowel, and renal agenesis diagnosed during her fetal ultrasound. Her abdominal examination reveals no masses, but is mildly tender. Her external genitalia appear normal, but she refuses an internal examination. Her pediatrician has given her a diagnosis of "cyclic vomiting syndrome" and is treating her with anti-nausea medication and antidepressants and has referred her to a psychiatrist. Her mother is at her wits end and is coming to you for a second opinion. You recommend:

- ☐ A Referral to a gastrointestinal specialist to control the vomiting
- ☐ B Karyotype to exclude a Y chromosome and risk for gonadoblastoma
- ☐ C Serum 17-hydroxyprogesterone level
- ☐ D Serum testosterone
- ☐ E Pelvic ultrasound

QUESTIONS 3–10

- ☐ A Swyer syndrome
- ☐ B MRKH
- ☐ C CAIS
- ☐ D 46XX gonadal dysgenesis
- ☐ E Uterus didelphys
- ☐ F Uterus didelphys, obstructed hemivagina
- ☐ G Transverse vaginal septum
- ☐ H Cervical agenesis
- ☐ I Imperforate hymen

- 3. Menstruation occurs despite tampon insertion
- 4. Estrogen replacement needed to induce puberty, gonads do not need to be removed
- 5. Estrogen therapy needed to induce puberty, gonads need to be removed at diagnosis
- 6. Karyotype 46XY, can carry a pregnancy conceived with donor oocytes
- 7. Associated with right renal agenesis
- 8. Must be distinguished from imperforate hymen
- 9. Must be differentiated from transverse vaginal septum
- 10. Associated with blue bulging introitus with valsalva due to obstruction

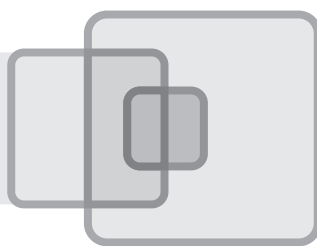


Answers and Explanations

1. **The answer is C** [III C, IV A]. MRKH represents abnormal development of the müllerian structures in a 46XX individual. The vagina and uterus are underdeveloped or absent, but the ovaries are not affected and are normal. The ovaries produce normal levels of testosterone for a female. Both the axillary and pubic hair are normal for a female as the androgen receptors are intact. Pregnancy is possible with a gestational carrier as the oocytes are normal and can be fertilized and transplanted into a surrogate uterus. With CAIS the testosterone levels are normal for a male, but there is scant or absent axillary and pubic hair as the androgen receptor is nonfunctional. The gonads are testes and should be removed after puberty due to the increased risk of malignant transformation. There is no vagina or uterus because the testes did produce antimüllerian hormone during embryonic development. Pregnancy with gestational carrier is not possible as the testes do not function normally and do not produce sperm or contain oocytes.

2. **The answer is E** [III B 1 a]. This young woman has increasingly severe dysmenorrhea, associated with nausea and vomiting and has a history of congenital renal agenesis. Therefore, she has a müllerian anomaly until proven otherwise. An ultrasound is the next step. If ultrasound is not able to distinguish the anatomy, then an MRI is recommended to exclude an obstructed lateral müllerian fusion defect. She most likely has a bicornuate/septate uterus with obstructed horn. Uterus didelphys with obstructed hemivagina is less likely as she has not masses appreciated on abdominal examination. The hormones tests are not relevant as she has normal menstrual cycles. A karyotype is also not necessary as she has normal external genitalia and normal menstruation.

3–10. **The answers are 3. E** [III A 4 a], **4. D** [IV F], **5. A** [IV C], **6. A** [IV C], **7. F** [III B 2], **8. G** [III C 2], **9. H** [III C 3], **10. I** [III C 1]. Uterus didelphys is usually associated with a longitudinal vaginal septum and two vaginal canals. With tampon insertion into one hemivagina, the other hemivagina is patent and therefore not occluded. The patient perceives this as tampons not working. With 46XX gonadal dysgenesis, the ovaries are nonfunctioning, but do not contain a Y chromosome. Breast development will need to be induced with estrogen, but the ovaries do not need to be removed. In contrast, with Swyer syndrome (46XY gonadal dysgenesis) the gonads are also not functioning, so breast development will need to be induced with estrogen, but the gonads do need to be removed due to Y chromosome and risk of gonadoblastoma. Since malignant transformation can occur at any time, gonadectomy should be performed at time of diagnosis. This is in contrast to CAIS where gonadectomy can be deferred to after puberty. To carry a pregnancy using donor oocytes, a uterus is necessary and nonfunctioning gonads would be present. This limits the choices to 46XX gonadal dysgenesis or Swyer syndrome. Since Swyer syndrome is defined as 46XY gonadal dysgenesis, this is the correct answer. Uterus didelphys with obstructed hemivagina is associated with right renal agenesis much more frequently than left. Transverse vaginal septum that is low needs to be distinguished from imperforate hymen as the surgical approach is different. Imperforate hymen just involves resection of hymenal tissue while transverse vaginal septum required resection of the septum with anastomosis of upper and lower vaginal canals. Cervical agenesis needs to be differentiated from high transverse vaginal septum as surgical resection of high vaginal septum is not associated with risk of infection as the cervix serves as a barrier to infection. With anastomosis of the vagina to the uterus, the protective barrier, the cervix, is not present and ascending infection from the vagina to the uterus and peritoneal cavity with subsequent death has been reported. For cervical agenesis, hysterectomy is often recommended. Imperforate hymen is associated with primary amenorrhea with cyclic or chronic pelvic pain often associated with a mass. If there is a large hematocolpos present that extends down to the introitus, then a blue hue bulge of the distended hymenal tissue can be seen with valsalva. If not such blue bulging tissue is seen, then imperforate hymen may not be the diagnosis.



Amenorrhea

JANET F. MCLAREN • CLARISA GRACIA

I

INTRODUCTION

A **Amenorrhea** is the absence of menses. It is classically described as primary or secondary. The differential diagnosis for amenorrhea is listed in Table 22–1.

1. **Primary amenorrhea** is the absence of menses by the age of 13 years in girls who do not show signs of developing secondary sexual characteristics, or by the age of 15 years in girls with normal development of secondary sexual characteristics. The age of work-up has decreased slightly over the past years due to a secular trend of earlier onset of menarche.
2. **Secondary amenorrhea** is the cessation of menses for a period of 6 months or a three-cycle interval in women who have been menstruating regularly.

B **Normal menstrual cycle physiology** requires interaction between the hypothalamus, pituitary gland, ovaries, and uterus.

1. Hypothalamic *pulsatile* release of gonadotropin-releasing hormone (GnRH) stimulates secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary.
2. FSH stimulates a cohort of ovarian follicles to undergo growth and development.
3. LH stimulates theca cells to produce androgens, which are converted to estrogens in granulosa cells by the enzyme aromatase.
4. Increasing estradiol levels exert negative feedback on FSH, and the follicle with the most FSH receptors becomes dominant. Other follicles undergo atresia. Estrogen also acts on the endometrium where it stimulates gland proliferation.
5. Increasing levels of estradiol exert positive feedback on LH secretion from the pituitary, resulting in the *LH surge*. Shortly after LH levels peak, ovulation occurs.
6. Granulosa cells produce progesterone during the luteal phase, resulting in luteinization of endometrial glands to their secretory form in preparation for a pregnancy. If pregnancy is not established, the corpus luteum regresses, progesterone support is withdrawn and menses ensues.

II

CLASSIFICATION AND ETIOLOGY OF AMENORRHEA

A **Categories** The etiologies of amenorrhea can be classified by serum gonadotropin levels.

1. **Hypergonadotropic:** elevated gonadotropins (typically FSH more than 20 IU/L; LH more than 40 IU/L), associated with low estradiol (less than 30 pg/mL)
2. **Hypogonadotropic:** low gonadotropin levels (typically FSH and LH less than 5 IU/L) associated with low estradiol (less than 30 pg/mL)
3. **Eugonadotropic:** normal gonadotropin levels (typically FSH and LH of 5 to 20 IU/L) associated with a normal estradiol

B **Hypergonadotropic amenorrhea** refers to conditions with lack of hormonal production from the gonad with resulting high gonadotropin levels. This condition typically results from ovarian failure and/or *gonadal dysgenesis*.

TABLE 22–1 Differential Diagnosis for Amenorrhea

Hypergonadotropic	Hypogonadotropic	Eugonadotropic
Premature ovarian failure	Functional/hypothalamic	Androgen excess
45,X or mosaic	Anorexia	PCOS
Carriers of fragile X	Female athlete triad	Late onset adrenal hyperplasia
Autoimmune causes	Stress	Complete androgen insensitivity
Infectious (mumps)	Chronic illness	Uterus/outflow tract anomalies
Metabolic causes	Kallmann syndrome	Müllerian agenesis (MRKH)
Chemotherapy/radiation	Pituitary tumor	Cervical agenesis
Gonadal dysgenesis	Craniopharyngioma	Transverse vaginal septum
45,X	Pituitary adenoma	Imperforate hymen
Swyer syndrome	Sheehan's syndrome	Asherman's syndrome
46,XX gonadal dysgenesis	Delayed pituitary	
Resistant ovary syndrome	Iatrogenic	
Infiltrative disease	Hormone therapy	
	Dopamine drugs	
	Brain radiation	

1. Premature ovarian insufficiency

a. Previously referred to as premature ovarian failure. It is defined as secondary amenorrhea with ovarian failure before 40 years of age.

b. Causes include:

(1) Genetic:

(a) 45,X or 45,X/46,XX (see below)

(b) Deletions in distal segment of the long arm of the X chromosome

(c) Fragile X carriers. Fragile X premutation is associated with premature ovarian insufficiency and is caused by an increased number (55 to 200) of trinucleotide repeats on the X chromosome

(2) Autoimmune disease: Typically autoimmune ovarian insufficiency is highly correlated with and can follow autoimmune adrenal insufficiency. The most common autoimmune disease seen with premature ovarian insufficiency is thyroid disease as it is the most common autoimmune disease. Other autoimmune diseases seen with autoimmune premature ovarian insufficiency include hyperparathyroidism, pernicious anemia, myasthenia gravis, and diabetes. **The following laboratory studies may be helpful in establishing the diagnosis of autoimmune ovarian insufficiency: fasting glucose, thyroid-stimulating hormone (TSH), thyroid antibodies, anti-adrenal antibodies, calcium, phosphorus, complete blood count, and AM cortisol**

(3) Infectious (e.g., mumps)

(4) Metabolic: Galactosemia is an autosomal recessive deficiency in galactose-1-phosphate uridylyltransferase. The accumulated galactose metabolites is toxic to the ovary, and decreases the number of oögonia

(5) Iatrogenic: Chemotherapy (especially alkylating agents) or pelvic radiation

2. **Gonadal dysgenesis** is the abnormal development of the gonad. This typically results from a chromosomal anomaly, the most common of which is 45,X. Patients with Y-bearing cell lines should undergo a gonadectomy as they are at increased risk of a germ cell malignancy (e.g., dysgerminoma, gonadoblastoma, and choriocarcinoma).

a. **Turner syndrome**

(1) The most common genotype is 45,X, which is accompanied by nonfunctional streak ovaries and primary amenorrhea. Mosaicism (45,X/46,XX) may occur; these women may have some ovarian function through early adulthood, and may become pregnant, but then progress to secondary amenorrhea.

(2) In general, 10% to 20% of cases have spontaneous puberty, and 2% to 5% of cases have spontaneous menses.

- (3) Phenotypic characteristics include short stature, webbed neck, shield chest, and increased carrying angle at the elbow. It is essential to rule out cardiovascular and renal anomalies in suspected cases.
 - (4) Streak gonads with Turner syndrome do not need to be removed as there is no Y chromosome present and no risk of malignancy.
 - b. 46,XY gonadal dysgenesis (Swyer syndrome)**
 - (1) Genotype is male (46,XY), but testes do not function so müllerian structures persist (no müllerian inhibiting substance), Wolffian ducts regress, and external genitalia are female.
 - (2) Hypogonadism results, and there is a lack of sexual development.
 - (3) Streak gonads are typically removed due to risk of malignant transformation.
 - c. 46,XX gonadal dysgenesis.** Similar to Turner syndrome, minus the somatic features.
 - 3. Resistant ovary syndrome**
 - a.** Rare disorder, due to defective gonadotropin *receptors* or a postreceptor signaling defect. On histology the ovaries are found to have follicles, but these follicles do not respond to gonadotropin stimulation.
 - b.** Results in amenorrhea in girls with otherwise normal growth and development.
- C Hypogonadotropic amenorrhea** results from deficient secretion of GnRH from the hypothalamus or deficient secretion of gonadotropins from the pituitary. As a result there is little or no hormone production from the ovaries, although the ovaries are normal and capable of producing hormones.
- 1. Functional amenorrhea** is a reversible disorder of impaired GnRH secretion which typically results from an energy imbalance: that is, energy expended exceeds energy taken in. GnRH is suppressed by a complex interplay of neuropeptides including leptin, CRH, and the endorphins. Etiologies include:
 - a. Anorexia**
 - (1) Anorexia occurs in 1% of all young women.
 - (2) Signs and symptoms include amenorrhea, bradycardia, dry skin, hypothermia, lanugo hair, constipation, and edema. Bulimia (binging and purging with vomiting, laxatives, or diuretics) may be seen in 50% of patients.
 - (3) About 17% body fat is necessary for initiating menarche; 22% is necessary to maintain menstrual regularity.
 - b. Female athlete triad.** This syndrome is defined as disordered eating, amenorrhea, and osteopenia or osteoporosis. This condition is usually associated with sports favoring a lean body type such as running, figure skating, gymnastics, and ballet. Although this is thought of as a disorder seen in elite athletes, high school and college athletes are also at risk.
 - c.** Stress: likely due to increased corticotrophin-releasing hormone
 - d.** Chronic illness
 - e.** Idiopathic
 - 2. Kallmann syndrome**
 - a.** The failure of olfactory axonal and GnRH neuronal migration from the olfactory placode in the nose to the hypothalamus, therefore there is no GnRH stimulation of the pituitary.
 - b.** Sporadic and genetic cases exist; inheritance can be X-linked, autosomal dominant, or autosomal recessive.
 - c.** Signs and symptoms include primary amenorrhea, normal karyotype, infantile sexual development, and the inability to perceive odors (anosmia or hyposmia).
 - d.** Possible coexisting features include bone and renal anomalies, cleft lip and palate, color blindness, or hearing deficit.
 - 3. Pituitary tumors.** Masses of the pituitary gland itself, or the surrounding structures, can effect hormone secretion. These tumors can be associated with visual changes, galactorrhea, and other hormone deficiencies, including hypothyroidism, amenorrhea, and adrenal insufficiency.
 - a. Craniopharyngioma**
 - (1) Tumor derived from Rathke's pouch, the infolding of the odontogenic epithelial layer which gives rise to the anterior pituitary during embryogenesis.
 - (2) Mass effect of these tumors can result in compression of the pituitary and pituitary stalk; other manifestations include visual field defects and blurry vision.

b. Pituitary adenomas

- (1) **Microadenomas** are less than 10 mm in size, **macroadenomas** are greater than or equal to 10 mm.
- (2) Adenomas may be functional or nonfunctional.
- (3) **Prolactinomas** are the most common functional pituitary adenoma that results in amenorrhea.
 - (a) Elevated prolactin causes amenorrhea by suppressing GnRH secretion.
 - (b) Treatment may involve dopamine agonist therapy (i.e., bromocriptine), surgery, or, in severe cases, radiation therapy.
- (4) **Cushing's disease** is caused by a functional adenoma in the pituitary that produces ACTH which stimulates production of cortisol from the adrenal gland and can also be associated with amenorrhea.

4. Sheehan syndrome

- a. Infarction of the pituitary gland, which typically occurs due to a postpartum hemorrhage.
- b. Typically presents with difficulty with lactation; results in panhypopituitarism.

5. Infiltrative disease. Hemochromatosis, histiocytosis, or other infiltrative processes can involve the hypothalamus and pituitary and result in amenorrhea.**6. Delayed puberty:** idiopathic or constitutional. Less common in girls than boys; there is often a family history of delayed puberty. Adrenarche and gonadarche are both delayed; normal pubertal development occurs, just at a later age.**7. Iatrogenic**

- a. Use of hormonal contraception, such as birth control pills, may result in amenorrhea due to thinning of the endometrial lining from the progesterone component. Amenorrhea may also temporarily occur after cessation of hormonal contraception, including progesterone-only forms like medroxyprogesterone (Depo-Provera).
- b. Drugs such as the phenothiazine derivatives, reserpine, and ganglia blockers can interfere with the levels of dopamine and norepinephrine; use of these agents can cause elevated prolactin levels which result in amenorrhea, usually associated with galactorrhea.
- c. Brain radiation can also damage the hypothalamus and pituitary; the pituitary is more radiosensitive.

D **Eugonadotropic amenorrhea** refers to conditions with either normal production of estrogen (hence normal gonadotropins) but lack of ovulation and therefore menstruation, or obstructive or hypoplastic anomalies of the uterus or outflow tract.

1. Disorders of androgen excess**a. Polycystic ovary syndrome:** (see Chapter 24)

- (1) A disorder of androgen excess, defined by two of the following three criteria in the absence of other causes for anovulation or androgen excess: Amenorrhea or oligomenorrhea signifying anovulation; clinical or laboratory evidence of hyperandrogenism; and the appearance of multiple small ovarian cysts on ultrasound ("**string of pearls**") or increased size of the ovaries.
- (2) Tonically elevated LH and low-normal FSH levels result in a failure to recruit a dominant ovarian follicle, the absence of ovulation, and increased androgen secretion from theca cells.
- (3) Patients are at increased risk of endometrial hyperplasia due to continued estrogen exposure and chronic anovulation.
- (4) A subset of patients with polycystic ovary syndrome (PCOS) have insulin resistance; as such, they are at increased risk for diabetes mellitus, obesity, and cardiovascular disease.
- (5) Losing 5% to 10% of body weight may allow patients to re-establish ovulatory cycles.

b. Late-onset congenital adrenal hyperplasia (CAH; see Chapter 25)

- (1) Also, a disorder of androgen excess, resulting from enzyme deficiencies in the steroid hormone pathway and excessive adrenal androgen production.
- (2) Severe forms of CAH present at birth with virilization and salt wasting; late-onset CAH presents in adolescence with hirsutism and menstrual irregularities, and is often confused with PCOS.
- (3) The most common form is 21-hydroxylase deficiency. The diagnosis can be made by measuring a morning serum 17-hydroxyprogesterone level.

2. Disorders of androgen receptors (see Chapters 21 and 25)

a. Androgen insensitivity syndrome (AIS; previously referred to as testicular feminization)

- (1) Defect of the androgen receptor. Patients are 46,XY, have male gonads and testosterone levels, but body does not respond to testosterone due to defective androgen receptor. The affected individual is phenotypically female.
- (2) Inheritance is X-linked recessive.
- (3) Patients have a blind vaginal canal and an absent uterus due to the presence of müllerian inhibiting substance produced by the testes. Testes may not descend, and can be positioned in the inguinal canal or labia. (The condition should be suspected in a female with bilateral inguinal hernias.)
- (4) **This condition must be differentiated from müllerian agenesis.** Patients with AIS will have sparse pubic and axillary hair, and testosterone levels will be in the male range. Breasts develop normally as significant testosterone is converted to estrogen.
- (5) Gonadectomy is recommended due to the risk of germ cell tumors, but may be deferred until after puberty to allow for normal growth. Malignancies in these patients do not typically present until the third decade.

3. Disorders of the uterus or outflow tract (see Chapter 21)

a. Müllerian agenesis (also known as Mayer–Rokitansky–Küster–Hauser [MRKH] syndrome)

- (1) The most common congenital anomaly of the uterus, occurs in 1 in 4,000 births.
- (2) The cause of this condition is poorly understood. Candidate genes include *WNT4* and *HOX 9, 10, 11, and 13*.
- (3) Absence or hypoplasia of the vagina, uterus, and tubes is characteristic.
- (4) Thirty-three percent of patients have urinary tract abnormalities, and another 12% have skeletal anomalies. A renal ultrasound is recommended to check for associated mesonephric anomalies.
- (5) Normal female testosterone level differentiates this disorder from complete androgen insensitivity.

b. Other müllerian anomalies

- (1) **Imperforate hymen.** This anomaly is not technically a müllerian anomaly since the hymen is derived from the urogenital sinus, but it functions and is treated as such. It occurs in 0.1% of female newborns, and may not present until 6 to 12 months after the menstrual lining sheds for the first time. The vagina may be distended with more than a liter of accumulated menstrual blood.
- (2) **Transverse vaginal septum.** This anomaly results in occlusion in the upper, middle, or lower segment of the vagina. These patients present with primary amenorrhea and episodic or cyclic pain symptoms.
- (3) **Cervical agenesis or dysgenesis.** Rare condition, which results in the obstruction of menstrual flow from the uterus to the vagina. These patients have similar presentation to those with transverse vaginal septum.

c. Asherman's syndrome

- (1) Acquired disorder of the uterus where an intrauterine surgical procedure or intrauterine infection results in scarring of the endometrial cavity.
- (2) Typically thought to result from a dilation and curettage in the setting of pregnancy and/or infection, however, can result from tuberculosis or other intrauterine infections that leave adhesions.
- (3) Symptoms include cyclic pain and bloating, in addition to absent or scant menses.

III

CLINICAL EVALUATION

A Human chorionic gonadotropin (hCG) The initial test for all women with primary or secondary amenorrhea should be an hCG level to evaluate for pregnancy.

B History A detailed history can help to elucidate the etiology of amenorrhea, and should include review of:

1. Pediatric growth and development charts.
2. Menstrual history including age of menarche, duration of menses, and symptoms.

3. Childhood or chronic illnesses and medication use.
4. Sexual history and use of illegal drugs.
5. Eating habits, exercise patterns, and self-image concerns.
6. Detailed review of systems, checking for the following conditions:
 - a. Hyperprolactinemia: galactorrhea and amenorrhea
 - b. Hyperthyroidism: nervousness, heart palpitations, weight loss, and heat intolerance
 - c. Hypothyroidism: fatigue, weight gain, and cold intolerance
 - d. Hypothalamic dysfunction or tumor: visual changes or hearing loss
 - e. Outlet obstruction: cyclic pain or bloating
 - f. Ovarian follicle depletion or dysfunction: vasomotor symptoms
 - g. Hyperandrogenic states: hirsutism or signs of virilization (e.g., clitoromegaly, deepening voice, and increased muscle mass)

C Physical examination These signs can also help to identify potential causes of amenorrhea. A complete examination should include:

1. Vital signs, including height and weight/body mass index
2. Palpate thyroid gland
3. Assess visual fields and cranial nerves (Kallmann syndrome or pituitary tumor)
4. Tanner staging of breast and pubic hair development to assess pubertal development, galactorrhea, or androgen excess
5. Abdominal examination, check for masses (e.g., pregnancy, distended vagina/uterus from outlet obstruction)
6. Pelvic examination, checking external genitalia for signs of virilization and normal female structures (vagina/uterus). Palpate adnexa to evaluate for an ovarian mass
 - a. If a pelvic examination is not possible or appropriate in the case of a young adolescent, an abdominal or pelvic ultrasound or a rectoabdominal examination can be used.
7. Check for Turner stigmata (e.g., short stature, webbed neck, or shield chest)

D Laboratory evaluation (Fig. 22–1)

1. **hCG** to evaluate for pregnancy as above
2. **TSH** to assess thyroid status
3. **Prolactin** to evaluate for prolactinoma
4. **FSH and estradiol:** to determine if patient is hypergonadotropic, hypogonadotropic, or eugonadotropic
 - a. In the case of hypergonadotropic amenorrhea, a karyotype should be checked; if normal, then evaluate for other autoimmune disorders.
 - b. In hypogonadotropic amenorrhea, an MRI should be obtained to rule out intracranial pathology.
 - c. In eugonadotropic amenorrhea, estrogen and progesterone withdrawal may be helpful to assess whether an outflow tract abnormality exists; imaging of the pelvis may also be useful.
5. Things to consider:
 - a. There is some overlap of FSH levels between hypogonadotropic and eugonadotropic causes of amenorrhea; a low-normal FSH level may prompt a work-up for etiologies in both categories, tailored by clinical findings.
 - b. In the patient with pubertal delay, a bone age is helpful to distinguish constitutional delay from true delayed puberty.

IV

MANAGEMENT

A Hypergonadotropic amenorrhea

1. **Hormone replacement therapy** is used to prevent bone loss, vasomotor symptoms, and urogenital atrophy due to lack of estrogen. Higher doses should be given to young reproductive age woman than given to women in the menopausal age to maintain secondary sexual characteristics and foster improvement or maintenance of bone density.

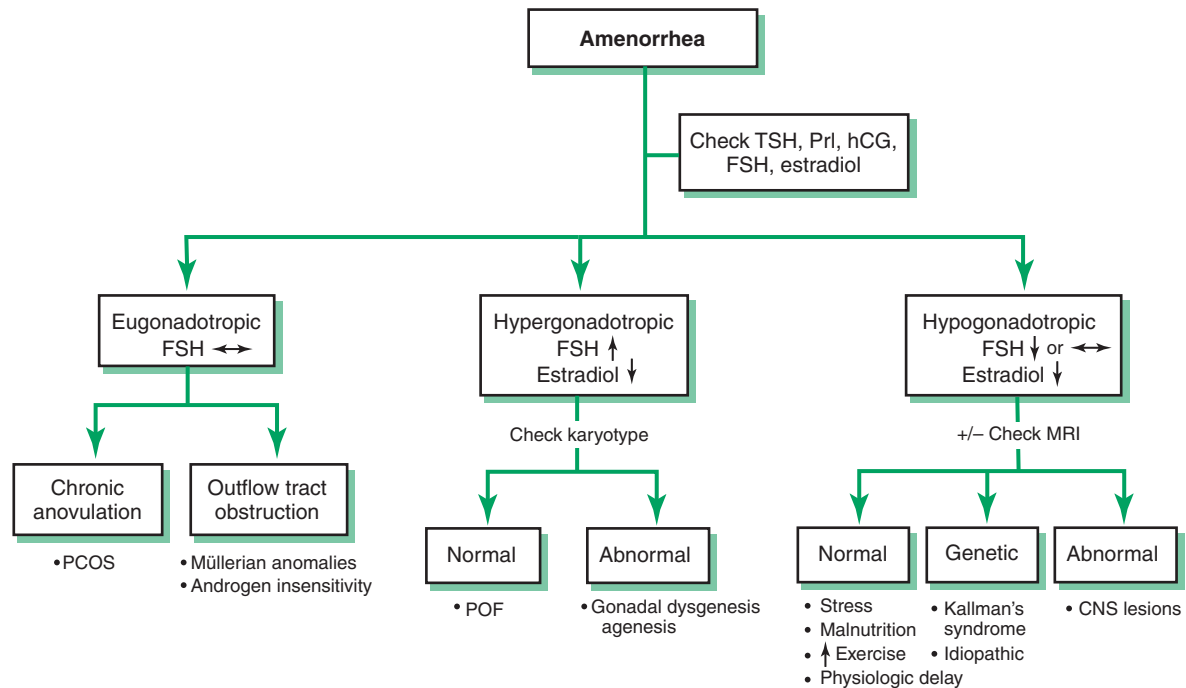


FIGURE 22-1 The evaluation of amenorrhea. CNS, central nervous system; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; MRI, magnetic resonance imaging; PCOS, polycystic ovary syndrome; POF, premature ovarian failure; Prl, prolactin; TSH, thyroid-stimulating hormone.

a. Estrogen replacement therapy

- (1) Conjugated estrogens or estradiol may be used.
- (2) Estrogen therapy is appropriate for women without a uterus; unopposed estrogen therapy in women with a uterus may lead to endometrial hyperplasia or cancer, so women with a uterus should use combined hormone therapy.

b. Combined hormone replacement therapy

- (1) Estrogens are used in combination with a progestin to protect the endometrium against hyperplasia or cancer.
- (2) Oral contraceptive pills (OCP) or hormone replacement therapy (HRT) formulations may be used; OCPs are preferred in women who do not desire pregnancy as HRT does not provide adequate contraception.

2. Removal of Y-containing gonads

- a. Patients with a Y-containing karyotype should undergo a gonadectomy due to the risk of malignancy in the testicular tissue (e.g., gonadoblastoma, dysgerminoma, yolk sac tumor, or choriocarcinoma).
- b. The gonad should be removed as soon as it is detected, except in the case of androgen insensitivity syndrome where gonadectomy can be deferred to allow natural puberty to occur.

3. Pregnancy

- a. It is unlikely, but not impossible, for women with premature ovarian failure to become pregnant due to sporadic ovulation. Hormone replacement and contraception should be discussed with these women accordingly.
- b. Assisted reproduction with oocyte donation can be an option for these patients.

B Hypogonadotropic amenorrhea Treatment is directed at the underlying cause of the hypogonadism and appropriate hormone replacement. In the case of intracranial tumors or adenomas, medical or surgical measures may be necessary.

1. Hormone replacement therapy

- a. As in hypergonadotropic amenorrhea, hormone replacement is needed to support bone health if lifestyle changes (e.g. weight gain, exercise activity) do not correct the low estrogen level.
- b. Oral contraceptives provide both hormonal replacement and contraception.

2. Pregnancy

- a. These patients typically do not respond to oral ovulation induction agents such as clomiphene citrate; in cases of borderline functional amenorrhea it is worth trying clomiphene given its low cost and lower risk profile compared to gonadotropins.
- b. Many will require gonadotropin therapy, which is available in purified urinary and recombinant forms and is administered by injection. A GnRH pump may also be used; however, availability of this device is limited in the United States.

3. Pituitary tumors

- a. Asymptomatic nonfunctioning adenoma
 - (1) Close surveillance is usually sufficient.
 - (2) Treatment with surgery is necessary with symptom occurrence or growth of the adenoma.
- b. Prolactinoma
 - (1) Usually the initial approach is medical therapy with a dopamine agonist (bromocriptine or cabergoline).
 - (2) For macroadenomas, transsphenoidal resection of the pituitary may be required if medical management fails. In rare cases, surgery may be combined with radiation therapy.
- c. Craniopharyngiomas and other central nervous system tumors are usually managed with surgical resection.

- 4. **Hypothyroidism.** Hypothyroidism is treated with thyroid hormone replacement, which re-establishes ovulatory cycles.

C Eugonadotropic amenorrhea Treatment of disorders of androgen excess involves symptom control; congenital müllerian anomalies or other structural disorders of the uterus or outflow tract typically require surgery.

1. Disorders of androgen excess**a. Polycystic ovary syndrome**

- (1) Menstrual cycle control. This typically can be achieved with combined oral contraceptive pills. Cyclic progesterone is another option; it should be given for 10 to 14 days duration at least every 3 months to ensure endometrial protection. Some patients will resume a normal menstrual cycle with metformin therapy.
- (2) Infertility. Ovulation induction can be achieved with clomiphene, letrozole, or metformin. Metformin is sometimes used in combination with clomiphene, especially in clomiphene-resistant patients. If oral ovulation induction fails, gonadotropins are another option, as is laparoscopic ovarian drilling.
- (3) Hirsutism/acne. Oral contraceptives can help with androgenic symptoms as ovarian production of androgens is suppressed and the estrogen component of the pill increases sex hormone-binding globulin, which decreases the amount of free circulating androgen. Anti-androgen drugs are an option, as is depilatory measures (shaving, electrolysis).
- (4) Combined oral contraceptive pills also provide contraception.

b. Late-onset congenital adrenal hyperplasia

- (1) The production of excess androgen is stopped by glucocorticoid therapy; steroid replacement should correct the androgen excess with return of menstrual cyclicity.
- (2) If this fails, options for menstrual cycle control, infertility, and management of androgenic symptoms are similar to those listed above for PCOS.

2. Complete androgen insensitivity

- a. Testes are non-functional in these XY patients, and should be removed after puberty/obtaining adult stature as outlined above.
- b. Hormone (estrogen) replacement therapy is required following gonadectomy. Progesterone is not necessary as there is no uterus.
- c. A neovagina can be created using dilators or surgical techniques.

3. Congenital müllerian anomalies

- a. In the absence of a uterus and vagina, a neovagina may be created by either a surgical procedure or the use of graduated dilators. This requires motivation on the part of the patient.

- b. Obstructed non-communicating uterine horns need to be surgically removed; a transverse vaginal septum or imperforate hymen is also corrected surgically. A transverse septum can be thick, in which case ultrasound-guidance can help with the reconstruction of the vagina.
 - c. Cervical agenesis is usually treated by removal of the abnormal cervix and uterus. Surgically connecting the uterus to the vagina to allow future pregnancy has been reported but carries the risk of multiple surgeries to maintain a patent outflow tract, infection, and death.
 - d. Ovaries are present as they do not derive from müllerian structures. Therefore, hormone replacement is not required and it is possible for these individuals to have biologic children through in vitro fertilization and a gestational carrier.
4. **Asherman's syndrome**
- a. Adhesiolysis may be performed hysteroscopically under direct visualization.
 - b. After the adhesiolysis, estrogen therapy can be considered to promote regrowth of the endometrial lining, especially in a hypoestrogenic patient. One regimen involves high-dose estrogen therapy postoperatively for 3 to 4 weeks, overlapping at the end of the month with a course of progestin.
 - c. Another consideration is the placement of an intrauterine pediatric Foley balloon with 2 to 3 mL of fluid for 3 to 5 days following surgery to prevent adhesion reformation.



Study Questions for Chapter 22

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A 15-year-old girl presents to your office with her mother because she has never had a period. They report that she seemed to grow and develop breasts at the same time as the other girls in school, but that she has not yet started to menstruate. She is active in sports at her school and plays the piano. She is 5'4", 128 lb; an examination reveals Tanner IV breast and pelvic examination reveals a blind vaginal pouch. Ultrasound confirms absence of a uterus. An FSH level is normal at 5.8 mIU/mL. The next step in the evaluation is:

- ☐ A MRI of the pituitary
- ☐ B Karyotype
- ☐ C Visual field testing
- ☐ D Trial of estrogen/progesterone to stimulate bleeding
- ☐ E Creation of a neovagina using graduated dilators

2. A 24-year-old female comes in for a new patient visit with the complaint of missed menstrual cycles. She states her period has never been regular, and that in the past it was common for her to skip a month or two between cycles. Now, however, she has not had a period in the past 7 months. She denies sexual activity, reports no medical problems, and her only prescribed medication is a face wash for acne. On review of systems she reports a weight gain of 10 lb over the past year. Her laboratory test reveals an FSH level of 8.7 mIU/mL, LH of 22.2 mIU/mL, estradiol of 45 pg/mL, TSH of 2.2 mIU/mL, prolactin of 12 ng/mL, and total testosterone of 98 ng/dL. The most likely diagnosis is:

- ☐ A Premature ovarian insufficiency
- ☐ B Polycystic ovary syndrome
- ☐ C Prolactinoma
- ☐ D Functional hypothalamic amenorrhea
- ☐ E Hypothyroidism

3. A 27-year-old woman presents to your office complaining of not getting her period. She came off of the birth control pill 9 months ago to attempt pregnancy and has not had a period since. Multiple home pregnancy tests have been negative. She states she underwent menarche at the age of 12 years, and that she did not always get a period every month during high school but was told this was normal because she was an athlete. She continues to be very athletic, running 5 to 6 times per week and also bikes. She is 5'6" and 124 lb and has no hirsutism or acne. The most likely reason for her amenorrhea is:

- ☐ A Polycystic ovary syndrome
- ☐ B Müllerian agenesis
- ☐ C Functional hypothalamic amenorrhea
- ☐ D Prolactinoma
- ☐ E Swyer syndrome

4. A 32-year-old woman returns to your care 5 months after the birth of her child. She had a postpartum hemorrhage following vaginal delivery of her son, requiring emergency surgery and multiple blood transfusions. She complains of fatigue, constipation, and states that her periods have not returned despite the fact that she has not been able to breastfeed. Her laboratory test reveals an FSH level of 1.2 mIU/mL, TSH of 0.3 IU/mL, and prolactin of 1 ng/mL. The most likely etiology of her secondary amenorrhea is:

- ☐ A Asherman's syndrome
- ☐ B Polycystic ovary syndrome
- ☐ C Functional hypothalamic amenorrhea
- ☐ D Sheehan's syndrome
- ☐ E Kallman's syndrome

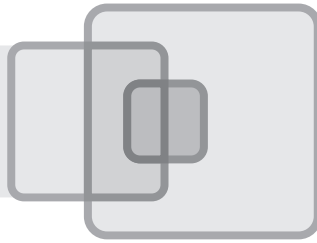
5. A 26-year-old female is referred to your office by her primary care doctor. She reports regular menses in the past, but has not had a period for 2 years. She did not bleed after a course of progesterone prescribed by her doctor. On examination she is 58 inches tall, has normal secondary sexual characteristics. Laboratory test reveals an FSH level of 82 mIU/mL and estradiol of 26 pg/mL. What is the next step in her evaluation?

- ☐ A Pelvic ultrasound
- ☐ B Total testosterone
- ☐ C Karyotype
- ☐ D Pituitary MRI
- ☐ E Trial of oral contraceptive pills



Answers and Explanations

1. **The answer is B.** In this patient with primary amenorrhea, breast development, and a blind vaginal pouch, the most appropriate next step is a karyotype to differentiate between müllerian agenesis and complete androgen insensitivity. A testosterone level can also be used to differentiate between the two; however, this was not listed as an option. Absence of pubic and axillary hair is seen with complete androgen insensitivity, and can also be used to differentiate from müllerian agenesis, but confirmation with testosterone or karyotype is necessary. It is key to differentiate müllerian agenesis from complete androgen insensitivity as it is imperative to remove the Y-containing gonad in the latter due to the risk of a germ cell malignancy in this tissue.
2. **The answer is B.** This woman fits the criteria for PCOS with her amenorrhea and clinical (acne) and biochemical hyperandrogenism (testosterone is elevated). Premature ovarian insufficiency would be suggested by elevated FSH, not LH. Her LH is elevated, but this elevated LH to FSH ratio is often seen with PCOS. Her laboratory test is not consistent with hypothyroidism, a prolactinoma or hypothalamic amenorrhea.
3. **The answer is C.** The most likely explanation for this patient's amenorrhea is functional hypothalamic amenorrhea given her reported exercise routine and height and weight. PCOS is another possible explanation, but is less likely given; she is underweight and lacks any signs of androgen excess. A prolactinoma would also be on the differential, but she does not report galactorrhea. Müllerian agenesis is ruled out as this is a case of secondary amenorrhea; she had menstrual cycles in the past.
4. **The answer is D.** This patient presents with a classic story for Sheehan's syndrome, or infarction of the pituitary caused by profound postpartum hemorrhage. Her inability to breastfeed is a classic presentation of this disorder. Her symptoms of fatigue and constipation in addition to amenorrhea suggest panhypopituitarism not just functional hypothalamic amenorrhea, and laboratory test confirms this suspicion with profoundly low thyroid and prolactin levels in addition to suppressed gonadotropins. Asherman's syndrome could be an explanation for her amenorrhea given her surgical procedure; however, it would not explain her low FSH or other symptomatology.
5. **The answer is C.** This patient presents with premature ovarian insufficiency since her laboratory testing reveals an elevated FSH with a low estradiol. A karyotype is the next step in any woman who presents with premature ovarian insufficiency under the age of 30. Given her short stature and secondary amenorrhea, she most likely has a mosaic Turner's syndrome (45X/46XX). When requesting a karyotype, it is important for the laboratory to know you are looking for a mosaic pattern as more metaphase spreads need to be counted. If the karyotype was normal, then testing for autoimmune ovarian insufficiency would be indicated. Pelvic ultrasound would not be the first test. Total testosterone would not be indicated unless there were signs of hyperandrogenism. A pituitary MRI would be indicated with low gonadotropins associated with low estradiol (hypogonadotropic amenorrhea). A trial of oral contraceptive pills would just tell you she has a uterus and patent outflow tract but would not help diagnose the cause of her amenorrhea. However, combined oral contraceptive pills can be used as treatment for premature ovarian insufficiency.



Abnormal Uterine Bleeding

CATHERINE SALVA

I

DEFINITIONS

- A** **Abnormal uterine bleeding** is defined as menstrual bleeding that is not regular and cyclic and “normal.” There are several terms used to describe and distinguish abnormal uterine bleeding patterns. **Menorrhagia** is prolonged or excessive uterine bleeding that occurs at regular intervals with a loss of more than 80 mL/cycle or bleeding that lasts for more than 7 days. **Metrorrhagia** is irregular menstrual bleeding or bleeding that occurs between regular cycles. **Menometrorrhagia** is irregular menstrual bleeding or bleeding that occurs between regular cycles, that is, excessive in amount or duration. **Polymenorrhea** is regular menstrual bleeding that occurs every 21 days or less. **Hypomenorrhea** is regular menstrual bleeding with unusually light flow. **Oligomenorrhea** is regular menstrual cycles that occur more than 35 days apart.
- B** Most causes of abnormal uterine bleeding can be divided into **structural causes** and **hormonal causes**. Structural and hormonal causes of abnormal bleeding can be present at the same time. Bleeding from other sources in the genital tract and systemic illnesses that cause bleeding must also be considered in the differential of abnormal uterine bleeding (see Table 23–1). These conditions are covered in detail in other chapters of this book.
- C** **Structural causes** of abnormal uterine bleeding include fibroids, endometrial polyps, adenomyosis, and malignant tumors of the uterus including sarcoma or endometrial cancer. Structural lesions can alter the muscle or lining of the uterus to cause **menorrhagia**, **metrorrhagia**, or **menometrorrhagia**.
- D** **Dysfunctional uterine bleeding (DUB)** describes abnormal uterine bleeding that occurs when there is a disruption of the cyclic hormonal changes that regulate the menstrual cycle. The term DUB is used to describe **anovulatory uterine bleeding** that occurs in the absence of any systemic medical illness or pelvic pathology. A disturbance in normal ovulatory function leads to **abnormal hormonal stimulation** of the endometrial lining of the uterus and causes bleeding that can be excessive, prolonged, and unpredictable.

II

PHYSIOLOGY OF NORMAL MENSTRUAL BLEEDING

- A** **Normal menstrual cycle characteristics** (see Chapter 19)
 - 1. **Purpose of the menstrual cycle.** During the menstrual cycle, multiple organs participate in the orderly and cyclic production of hormones, resulting in:
 - a. The recruitment and release of an oocyte by the ovary
 - b. Proliferation and differentiation of the uterine endometrium in preparation for implantation of an embryo in the uterus
 - c. Menstrual bleeding occurs in cycles where a pregnancy does not occur
 - 2. **Cycle length.** Most cycles range in length from 24 to 35 days. Fewer than 2% of women have regular menstrual periods more often than every 21 days or less often than every 35 days.
 - 3. **Cycle regularity.** Although the length of the menstrual cycle may vary from woman to woman, it usually remains the same in a particular individual.

TABLE 23–1 Differential Diagnosis of Abnormal Uterine Bleeding

Reproductive Tract Pathology	Aspirin	Premature ovarian failure
Cervicitis	Anticoagulants	Luteal phase defect
Cervical neoplasia	Psychotropic medications	Shortened follicular phase
Endometritis		Prolonged corpus luteum function
Endometrial polyps	Systemic Disease	
Endometrial hyperplasia	Hematologic disorders	Pregnancy-Related Conditions
Endometrial cancer	Thrombocytopenia	Normal pregnancy
Uterine leiomyomas	Von Willebrand disease	Threatened abortion
Uterine sarcomas	Hepatic disease	Spontaneous/incomplete abortion
Adenomyosis	Renal disease	Ectopic pregnancy
Ovarian neoplasms (hormone producing)	Endocrine Gland Dysfunction	Gestational trophoblastic neoplasm
	Hypothyroidism	
Medications	Hyperthyroidism	Trauma
Estrogen administration	Pituitary adenoma	Laceration
Combined hormonal contraception		Foreign body
Progestin-only contraceptive	Ovulatory Dysfunction	
Contraceptive intrauterine device	Anovulation	
	Polycystic ovary syndrome	

- a. The **follicular phase** represents the first-half of the menstrual cycle and is the source of the **person-to-person variation** in cycle length. The follicular phase begins with the onset of menses and culminates in the ovulation of a mature oocyte.
- b. The **luteal phase** is the second-half of the cycle and is more consistent in length, lasting **12 to 14 days in most individuals**. If a woman has a 28-day cycle, she tends to ovulate on or about Day 14 (and has a 14-day follicular phase); if a woman has a 35-day cycle, she tends to ovulate on or about Day 21 (with a 21-day follicular phase).

B **Postovulatory estrogen–progesterone withdrawal bleeding** describes the hormonal mechanism behind normal menstrual bleeding.

1. During the follicular phase of the cycle, the ovary produces **estrogen**, which results in growth of the uterine lining. The **follicular phase** of the ovary correlates with the **proliferative phase** of the menstrual cycle.
2. After ovulation, the **corpus luteum** develops from the remnant of the ovulatory follicle. The main function of the corpus luteum is to secrete **progesterone** (it also produces estrogen), which limits the estrogen-induced proliferation of the endometrium and causes it to stabilize. The **luteal phase** of the ovary corresponds to the **secretory phase** of the menstrual cycle, reflecting a postovulatory state.
3. If pregnancy does not occur, the corpus luteum regresses and hormonal support of the endometrium is withdrawn. Regression of the corpus luteum and the subsequent **decline in progesterone and estrogen** levels initiate a cascade of events that culminates in menstrual bleeding.

C **Onset of menstrual flow and its cessation** depend on hormonal changes as described above that signal a cascade of events.

1. **Initiation of menstrual flow** involves enzymatic autodigestion. Progesterone withdrawal stimulates an **inflammatory response**. **Lytic enzymes** are released from intracellular lysosomes, and matrix metalloproteinases are upregulated. This results in **breakdown of endometrial tissue** via degradation of extracellular matrix components and the basement membrane. Endometrial breakdown also leads to the release of significant quantities of **prostaglandins** (particularly $\text{PGF}_{2\alpha}$), which are potent mediators of myometrial contractions and vasoconstriction.
2. Rhythmic **vasoconstriction** of spiral arterioles leads to ischemia, necrosis, and **sloughing of the surface endometrium**. In addition to playing some role in the initiation of menses, local vasoconstriction plays a key role in the cessation of menstrual flow.

3. **Coagulation mechanisms** also aid in ending normal menstrual flow. **Thrombin** and **platelet plugging** of spiral arterioles also promote hemostasis.
4. **Estrogen production** at the beginning of a new menstrual cycle helps control bleeding by promoting growth of new lining to cover and heal the raw surface of the endometrium.

III

PATHOPHYSIOLOGY OF ABNORMAL UTERINE BLEEDING

- A** **Abnormal uterine bleeding** due to **structural causes** maintains the normal cyclic hormonal mechanisms as described above. Heavy or prolonged menstrual flow, or **menorrhagia**, can occur if a structural lesion distorts or increases the surface area of the endometrial cavity so as to interfere with the normal mechanisms involved in cessation of menses. Polyps or malignant tumors might have increased vasculature causing bleeding that is independent of the normal menstrual cycle, resulting in **metrorrhagia** or **menometrorrhagia**.
- B** **DUB** occurs with the disruption of cyclic hormonal changes that regulate the normal menstrual cycle. In up to 90% of cases it is a manifestation of anovulation leading to **estrogen breakthrough bleeding**. **Anovulatory uterine bleeding** and **DUB** are interchangeable terms.
1. In the absence of ovulation, **estrogen stimulates the endometrium** without the production of progesterone by the corpus luteum. As mentioned previously, progesterone is responsible for endometrial differentiation and also keeps stimulation of the endometrium in check.
 2. **Unopposed estrogen stimulation** of the endometrium leads to excessive glandular proliferation with lack of differentiation or development of stromal support. The result is an unstable, fragile, and heterogeneous endometrium that is prone to superficial breakdown and bleeding.
 3. As this pattern of unopposed estrogen stimulation continues, the **endometrium sloughs off in isolated locations**. These raw surfaces are restimulated by estrogen just as another part of the endometrium begins to slough off. Prolonged and excessive bleeding results.
 4. The **duration and level of unopposed estrogen** stimulation directly affect the amount and duration of bleeding.
 5. With the **loss of cyclic hormonal changes**, there is a disruption of the normal cascade of events that trigger the onset of menses. There is no periodic, orderly, self-limited shedding of the endometrium as **enzyme release**, **vasoconstriction**, **coagulation**, and **reepithelialization** are all affected by the lack of hormonal interplay.

IV

ETIOLOGY OF ABNORMAL UTERINE BLEEDING

- A** **Pregnancy-related bleeding** must be ruled out in any woman who is of reproductive age experiencing abnormal uterine bleeding because of its potentially life-threatening nature (Table 23–1). Pregnancy-related bleeding is covered in detail elsewhere in this book.
- B** **Structural causes** and/or **organic conditions**, such as polyps, uterine fibroids, endometritis, endometrial hyperplasia, and blood dyscrasias must be considered as possible causes of the bleeding. Fibroids, adenomyosis, and blood dyscrasias usually present with menorrhagia (i.e., excessive cyclic bleeding) since these lesions do not affect ovulatory function. Endometritis, cervicitis, endometrial polyps, and malignancies often present with irregular spotting or bleeding usually in addition to regular menstrual function.
- C** **DUB** or **anovulatory uterine bleeding** is caused by a disruption of the normal regulatory mechanisms that control the menstrual cycle. Ovulatory cycles result from a complex interaction of factors involving the hypothalamic–pituitary–ovarian axis. Abnormalities at any of these sites interfere with normal ovulation; a loss of normal ovulatory function occurs because of several causes.
1. Polycystic ovary syndrome (PCOS). **PCOS is the classic condition that causes DUB due to estrogen breakthrough bleeding** (see Chapter 24). This condition involves a complex set of endocrine derangements, including anovulation. It is present in 5% to 10% of women of reproductive age. PCOS is also associated with hyperandrogenism, insulin resistance, and often

obesity, each playing a role in the evolution of an oligo-ovulatory state. Women with PCOS are at increased risk for endometrial hyperplasia and endometrial cancer because of long-term unopposed estrogen stimulation of the endometrium.

2. **Immaturity of the hypothalamic–pituitary–ovarian axis.** Anovulation and DUB are often seen in postpubertal adolescents shortly after menarche and also seen in perimenopausal women. The onset of the first menstrual period may occur before the hypothalamic control mechanisms of ovulation are fully mature. Gonadotropin-releasing hormone (GnRH) secretion has not yet attained the pulsatile nature characteristic of ovulatory cycles. Estrogen breakthrough bleeding is often involved in these instances.
3. **Dysfunction of the hypothalamic–pituitary–ovarian axis.** Any factor that interferes with the normal pulsatile secretion of GnRH leads to anovulation. The following conditions typically cause anovulatory uterine bleeding; however, this is usually not due to estrogen breakthrough bleeding.
 - a. **Hyperprolactinemia.** Elevation of circulating prolactin may be caused by pituitary adenomas or a side effect of medications, most notably psychotropic drugs. Elevated prolactin inhibits normal GnRH pulsatility and results in anovulation.
 - b. **Stress and anxiety.** Anovulation and menstrual irregularities often occur during times of stress and major life changes. Loss of pulsatile GnRH secretion may occur as a result.
 - c. **Rapid weight loss.** Sudden and rapid weight loss from crash dieting may also interfere with normal GnRH secretion.
 - d. **Borderline anorexia nervosa.** Anovulation occurs early in the course of this disorder. If the anorexia increases in severity, complete loss of ovarian function may occur, resulting in amenorrhea and hypoestrogenism.
 - e. **Hypothyroidism.** This condition may also cause anovulation through dysregulation of a feedback loop that results in increased prolactin levels. Normal GnRH pulsatility is suppressed, as it is in primary hyperprolactinemia.
 - f. **Perimenopause.** This stage describes the years leading up to menopause. Women who are perimenopausal have very few oocytes remaining and as a result, ovulation is infrequent. The intervals between menstrual cycles lengthen as a result.
4. **Abnormalities of normal feedback signals.** Estradiol levels play a critical role in controlling the sequence of events during the normal ovulatory cycle. The rise and fall of estradiol at critical points in the cycle are important feedback mechanisms of cycle control. **Estradiol primarily exerts a negative feedback effect on follicle-stimulating hormone (FSH) secretion and must decrease appropriately before menses to allow the increase in FSH necessary for initiation of a new cycle.** Sustained estradiol levels at this time prevent normal cycling. Elevated estradiol levels can result from persistent secretion, abnormal clearance and metabolism, and production by extragonadal sources. **As in PCOS, estrogen breakthrough is often responsible for DUB in these patients.**
 - a. Certain medical conditions, most notably **hepatic disease or thyroid abnormalities**, may affect the metabolism and clearance of estradiol. The fluctuation in circulating estrogen levels seen in these conditions may cause ovulatory and menstrual dysfunction.
 - b. Conditions that lead to an increase in the production or conversion of estrogen precursors result in extragonadal production of estrogen. **Adipose tissue**, which contains aromatase, is capable of converting peripheral androgens to estrogens. This process increases with increasing body weight.
 - c. Estrogen-producing ovarian tumors such as granulosa cell tumors can cause disruption of the normal feedback mechanism.

D Hormonally related bleeding These patterns of abnormal uterine bleeding are hormonally related, but do not constitute DUB, or anovulatory uterine bleeding usually thought to be estrogen breakthrough bleeding. The following patterns are commonly seen and may be confused with DUB.

1. **Estrogen withdrawal bleeding.** This bleeding may occur at **midcycle** when estrogen levels decline briefly just before ovulation. Estrogen withdrawal also causes bleeding that occurs after bilateral oophorectomy.

2. **Progesterone breakthrough bleeding.** In the setting of prolonged progesterone administration, the endometrium receives relatively little estrogenic support. This occurs most often when women use progestin-only contraceptives for extended periods. The antagonistic effect of progesterone on the endometrium combined with inadequate estrogen stimulation results in atrophy. As a result, the endometrial surface bleeds irregularly, varying in amount and duration.

V

EVALUATION AND DIAGNOSIS OF ABNORMAL UTERINE BLEEDING

A History In general, structural causes of abnormal bleeding cause a change in the flow pattern of bleeding, but do not affect the menstrual cycle length. Dysfunctional bleeding, however, is defined as a disruption in ovulation and therefore causes a change in the length of the menstrual cycle or leads to an unpredictable and irregular bleeding pattern. A careful history can suggest which is most likely. Women may have structural and hormonal causes of abnormal bleeding present simultaneously, and both need to be diagnosed and addressed.

1. **Contraceptive use/pregnancy.** Pregnancy should always be ruled out in women of reproductive age even if they use contraception. All methods of contraception have small, inherent failure rates when used properly. This rate increases with faulty or erratic use. Moreover, some patients on hormonal contraception experience abnormal bleeding (e.g., progesterone breakthrough bleeding) that either resolves spontaneously or that can be remedied with estrogen therapy. Intrauterine devices (IUDs) may also be associated with abnormal bleeding due to local inflammation and/or progesterone breakthrough if the device contains a progestin.
2. **Current bleeding history.** It is critical to describe the current pattern of bleeding accurately and to determine to what extent it differs from previous bleeding patterns. Variations from normal cyclic patterns may be a sign of DUB.
3. **Menstrual history.** DUB is most commonly associated with either **oligomenorrhea** or **menometrorrhagia**. Age at menarche, cycle frequency and duration, and presence of cyclically occurring symptoms establish the presence or absence of ovulatory cycles and an intact hypothalamic–pituitary–ovarian axis. **Menorrhagia** or **intermenstrual bleeding** is often a sign of a structural or an organic cause of bleeding. A history of prolonged anovulation identifies women at risk for endometrial hyperplasia and cancer, requiring endometrial sampling.
4. **Medical history.** The presence of a medical condition contributing to abnormal uterine bleeding should be considered. Up to 20% of women presenting with menorrhagia will have an underlying bleeding disorder. Thirty percent of adolescents who present with severe blood loss have an associated coagulopathy, such as **von Willebrand disease**, in which platelets are dysfunctional. In addition, **thyroid disease** and **pituitary adenomas** may be the underlying cause of bleeding associated with anovulatory cycles.
5. **Medication history.** Certain medications may be associated with abnormal uterine bleeding (e.g., anticoagulants). Psychotropic medications may secondarily cause DUB through an elevation of prolactin.

B Physical examination A complete physical examination detects organic causes of abnormal uterine bleeding and signs associated with causes of anovulation and DUB.

1. **General physical examination.** Thyroid enlargement, galactorrhea (prolactinoma), ecchymosis, and purpura may be apparent. Pallor or vital sign instability suggests either brisk bleeding or long-standing bleeding with associated anemia. Such information helps guide the method and acuity of treatment.
2. **Gynecologic examination.** A complete gynecologic examination, including a Papanicolaou smear and a bimanual examination can give information regarding the presence of structural abnormalities. Elimination of anatomic or structural causes of abnormal bleeding is the first step in the diagnosis of DUB.

C Laboratory studies The history and physical examination determine the need for additional laboratory studies. Not all tests are necessary in all patients.

1. **Pregnancy test.** Modern urine pregnancy tests are highly sensitive, inexpensive, and easy to perform. Such tests should be performed in all premenopausal women with abnormal bleeding.

2. **Complete blood count.** A hemoglobin and hematocrit should be obtained in women with heavy or prolonged bleeding to evaluate for anemia. A white blood cell count may be useful in the diagnosis of endometritis; a platelet count detects thrombocytopenia.
3. **Thyroid-stimulating hormone (TSH) and prolactin.** Levels of these hormones should be obtained whenever bleeding is thought to be associated with anovulation.
4. **Coagulation profile.** Prothrombin time, partial thromboplastin time, and a workup for von Willebrand disease should be performed when an associated coagulation disorder is suspected.
5. **Androgen profile.** If there are signs of hyperandrogenism and oligo-ovulation or anovulation, a hyperandrogenic disorder should be considered and tested for appropriately (see Chapters 24 and 25).

D Diagnostic procedures The need for additional diagnostic testing is determined on an individual basis.

1. **Ultrasonography and sonohysterography.** Ultrasound evaluation of the uterus is useful for all cases of abnormal uterine bleeding. If a pelvic examination reveals an enlarged uterus, ultrasound can help distinguish uterine from ovarian masses or clarify between fibroids and adenomyosis. In cases of a normal gynecologic examination, ultrasound can often identify intrauterine polyps or submucosal fibroids that lead to heavy bleeding. The transvaginal approach is often more sensitive than the transabdominal approach. Sonohysterography, in which saline is instilled into the uterine cavity during transvaginal sonography, further enhances the ability to delineate intracavitary lesions.
2. **Endometrial biopsy.** Any woman older than 35 years who presents with abnormal bleeding should have an endometrial biopsy performed to rule out malignancy. Any woman of any age with prolonged anovulatory uterine bleeding is thought to be at increased risk of hyperplasia and cancer and should also undergo endometrial biopsy. Endometrial biopsy is performed as an office procedure using a small catheter to obtain the specimen. Endometrial hyperplasia, especially with atypical histologic features, is believed to be a precursor of endometrial carcinoma and can be treated medically or surgically. Cases of endometrial cancer should be referred to a gynecologic oncologist for further treatment.
3. **Dilation and curettage (D&C).** This procedure is warranted in those women who have DUB and do not respond to medical management with hormonal manipulation. D&C is also required when an endometrial biopsy cannot be performed in the office; this is usually the case if a woman has a stenotic cervical os, making it impossible to pass the biopsy catheter.
4. **Hysteroscopy.** Hysteroscopy involves **direct visualization of the endometrial cavity**. Hysteroscopy and D&C are routinely performed at the same time. Hysteroscopy is particularly useful when a polyp or submucosal fibroid is suspected, because these lesions can be confirmed and removed under direct visualization. After hysteroscopy, a D&C is performed to rule out coincident endometrial pathology whether a cavitory lesion is visualized or not.

VI

TREATMENT OF ABNORMAL UTERINE BLEEDING

A General principles The cause of the abnormal bleeding should determine the treatment options available to the patient. Hormonal or medical conditions causing the bleeding should be addressed. Structural causes are often addressed surgically (as in the case of fibroids, polyps, or cancers), but conservative therapies may also be appropriate. These treatment options are discussed elsewhere. Patients with structural and hormonal causes of their abnormal bleeding may need multiple or sequential therapies.

B Hormonal therapy The treatment of anovulatory DUB is hormonal therapy with a progestin, an estrogen, or a combination of the two. The choice of therapy is based on the duration of bleeding, age of the patient, and preference of the patient.

1. **Progestins. Progesterone supplementation** is the treatment of choice for women with DUB caused by estrogen breakthrough. Addition of progesterone restores the normal controlling influences to the endometrium. In addition, progestins act as antiestrogens. The **antimitotic**,

antigrowth effect of progestins supports their use in the treatment of **endometrial hyperplasia** caused by estrogen excess.

- a. **Progestins support and stabilize the endometrium** so that an organized sloughing of the endometrium occurs after its withdrawal.
 - b. Progestins may not stop an acute episode of DUB as effectively as estrogen, especially if bleeding has been prolonged. However, **progestin, either alone or in combination with estrogen**, is warranted for long-term control after the acute episode of DUB is controlled.
 - c. Types of orally administered progestins used to regulate bleeding are **Medroxyprogesterone acetate** 10 mg daily for 10 to 12 days, **norethindrone acetate** 5 mg daily for 10 to 12 days, or **oral micronized progesterone** 200 mg daily for 10 to 12 days. Oral progestins may be administered cyclically, daily, or as a high to low dose taper over 5 to 7 days.
 - d. The **levonorgestrel IUD** is very effective in reducing menstrual flow and is an excellent treatment option for women interested in long-term contraception. It requires replacement every 5 years. This IUD achieves progestin concentrations in the endometrium several hundred-fold higher than achieved with traditional systemic therapy. Up to 80% of users may become amenorrheic at 1 year due to progestin effects on the uterine lining. Treatment satisfaction rates in levonorgestrel IUD users are comparable to those in women who have undergone endometrial ablation.
 - e. Progestin injections (DMPA) administered intramuscularly or subcutaneously every 3 months or progestin contraceptive implants (lasting 3 years) can be considered for therapy in women interested in long-term contraception. However, these are not ideal for short-term induction of amenorrhea because of unpredictable **progesterone breakthrough bleeding** associated with early use.
2. **Oral contraceptive therapy.** Frequently, DUB is associated with prolonged endometrial buildup and heavy bleeding in younger women. Combined estrogen–progestin therapy in the form of oral contraceptives is used to treat episodes of acute bleeding. Combined oral contraceptives convert a fragile, overgrown endometrium into a structurally stable lining. Bleeding usually is controlled within 24 hours of initiation of therapy. If no response has occurred by this time, another treatment for the DUB should be pursued.
 - a. Any low-dose combination oral contraceptive can be used. The pill is administered two or three times a day for 3 to 4 days if excessive and prolonged bleeding is present.
 - b. A heavy withdrawal bleed is expected after cessation of therapy.
 - c. After the withdrawal bleed, cyclic therapy with once-a-day administration is continued for 3 months to reduce the endometrial lining to baseline levels. The oral contraceptive can be continued if birth control is desired.
 3. **Estrogens.** High-dose estrogen therapy rapidly stops bleeding within 12 to 24 hours. The acute mechanism of action is thought to be **initiation of clotting at the capillary level**. Proliferation of the endometrial surface is a later effect. It is especially useful when bleeding has been **prolonged** or is secondary to **progesterone breakthrough bleeding**.
 - a. **Conjugated estrogens** (1.25 mg) or **estradiol** (2 mg) are administered daily for 7 to 10 days. If bleeding is moderately heavy, the same doses are administered every 4 hours during the first 24 hours of therapy. Treatment is continued for another 10 days, with the daily dose of estrogen combined with 10 mg medroxyprogesterone. A withdrawal bleed is expected after cessation of therapy.
 - b. **Intravenous estrogen** is effective in treating **acute profuse DUB**. Estrogen (25 mg) is administered intravenously every 4 hours until the bleeding lessens, or up to 12 hours. A progestin must be started at the same time.
 - c. After the acute episode is controlled, **chronic therapy** is initiated with the oral contraceptive or periodic progesterone for at least 3 months.

C Medical therapy

1. **Nonsteroidal anti-inflammatory drugs (NSAIDs).** NSAIDs inhibit the synthesis of prostaglandins, which are substances that have important pharmacologic actions on the endometrial vasculature and on endometrial hemostasis. NSAIDs are primarily effective in limiting menstrual blood loss in women with ovulatory cycles, with a reduction in blood flow by as much as 50%.

2. **GnRH agonists.** After control of an episode of acute bleeding, GnRH agonists may help achieve amenorrhea in chronically ill patients. Expense and the long-term effects of hypoestrogenism limit therapy. If long-term therapy is chosen, hormone replacement therapy with estrogen and progestin is advised.
3. **Desmopressin.** A synthetic analog of arginine vasopressin, desmopressin stimulates the release of von Willebrand factor from endothelial cells.
4. **Antifibrinolytics.** Newer hemostatic agents such as *e*-aminocaproic acid and tranexamic acid inhibit the conversion of plasminogen to plasmin, to inhibit fibrinolysis and stabilize clots.

D Surgical therapy

1. **D&C with hysteroscopy.** This procedure can be a diagnostic and therapeutic modality. Endometrial polyps, submucosal fibroids, and endometrial hyperplasia can be treated with this procedure. This procedure is not the treatment of first choice in DUB but can be useful in cases of acute bleeding. It is also undertaken in patients who have bleeding refractory to medical therapy or who are not candidates for hormonal manipulation.
2. **Endometrial ablation.** Ablation of the endometrium is a surgical option for women who have unexplained menorrhagia or who have DUB but are not candidates for hormonal therapy or hysterectomy because of medical conditions or who wish to avoid hysterectomy but choose not to pursue hormonal therapy. It is not indicated in cases where there is endometrial hyperplasia or cancer, or an otherwise structural cause of the bleeding.
 - a. Ablation of the endometrium is performed using laser, electrocautery, or thermal destructive techniques.
 - b. Fifty percent of women achieve amenorrhea; 90% achieve a decrease in bleeding.
 - c. The long-term risk of the occurrence of undetectable endometrial carcinoma in isolated segments of endometrium has yet to be defined.
3. **Hysterectomy.** This procedure is a realistic treatment option in the following situations:
 - a. For women who have completed childbearing in whom persistent abnormal bleeding is often worrisome or life threatening
 - b. For women who do not tolerate medical management
 - c. For women diagnosed with atypical endometrial hyperplasia and with an increased risk of endometrial cancer, who may opt for surgical as opposed to medical management



Study Questions for Chapter 23

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A 51-year-old woman, gravida 1, para 1, presents to your office with complaints of heavy menstrual flow that has been persistent over the last 6 weeks, occurring after a 7-month break from her periods. Her periods were monthly and regular until the age of 46 years. Review of systems is negative and she specifically denies lightheadedness. Her speculum examination is unremarkable. The bimanual examination reveals a slightly enlarged, regular contour, anteverted uterus that is nontender to palpation. The next best step in management is:

- ☐ A Low-dose oral contraceptive pills
- ☐ B Endometrial biopsy
- ☐ C Dilation and curettage
- ☐ D Endometrial ablation
- ☐ E Levonorgestrel IUD

2. A 34-year-old woman, gravida 0, presents to you reporting bleeding between her periods with cycles that seem irregular and more than 40 days apart. She has never had monthly periods. She is bothered by acne as well as hair growth on her face, chest, and abdomen. She would like to become pregnant. She denies any medical problems but states that her doctor has advised her to lose weight because of borderline diabetes. She is 5 feet 4 inches tall and weighs 230 lb. Her gynecologic examination is unremarkable. The most likely explanation for her abnormal uterine bleeding is:

- ☐ A A testosterone-secreting tumor of the ovary or adrenal
- ☐ B Increased exogenous progesterone
- ☐ C Polycystic ovary syndrome
- ☐ D Increased exogenous estrogen
- ☐ E Loss of pulsatile GnRH due to thyroid dysfunction

3. A 14-year-old nulligravid girl presents to the emergency department by ambulance because she passed out on the floor of her house and is covered in blood. She is now conscious. She has been bleeding off and on for the past 5 months since onset of menarche. Her BP = 98/48, P = 106, RR = 16, and T = 96.2. Physical examination is unremarkable. Pelvic ultrasound is also unremarkable. Serum human chorionic gonadotropin (hCG) is negative, and her hemoglobin is 7 g/dL. You begin a low-dose combination oral contraceptive taper. The next best step in management of this patient is:

- ☐ A Endometrial biopsy
- ☐ B Reassurance
- ☐ C NSAIDs
- ☐ D Hysteroscopy and dilation and curettage
- ☐ E Coagulation profile

4. A 26-year-old woman presents complaining of intermenstrual spotting over the last 3 months, accompanied by minimal flow during her menses. She has been taking the same low-dose combined oral contraceptive faithfully for the last 5 years. Her physical examination is unremarkable. The most probable explanation for her symptoms is:

- ☐ A Endometrial hyperplasia
- ☐ B Progesterone breakthrough bleeding
- ☐ C Pregnancy
- ☐ D Bleeding disorder
- ☐ E Estrogen breakthrough bleeding

5. A 46-year-old woman, gravida 6, para 4, presents complaining of a 2-year history of heavy menstrual flow lasting 9 days, with occasional episodes of soaking her clothes and bedsheets with menstrual blood. She has a history of bilateral tubal ligation. Her menses are occurring every 26 days, and she denies any bleeding between menses. The rest of her history is unremarkable. The test most likely to aid in diagnosis would be:

- ☐ A Menstrual calendar
- ☐ B Pregnancy test
- ☐ C Endometrial biopsy
- ☐ D Pelvic ultrasound
- ☐ E TSH



Answers and Explanations

1. The answer is B [V D 2]. The risk of endometrial carcinoma increases with age and should be ruled out in any woman older than 35 years that presents with abnormal uterine bleeding. Endometrial biopsy should be performed. Many women who are perimenopausal have erratic bleeding because of the transition from regular ovarian folliculogenesis and hormone production to relative ovarian quiescence. In addition, endometrial hyperplasia often develops in women with a history of chronic anovulation and unopposed estrogen stimulation of the endometrium, as this woman's menstrual history may suggest. Endometrial hyperplasia can be treated with progestin therapy. When a woman is diagnosed with endometrial hyperplasia with atypia, she has an increased risk for endometrial carcinoma. Dilation and curettage would be the next step after an endometrial biopsy if the results are not satisfactory (e.g., cervical stenosis and inability to obtain biopsy in the office or no tissue obtained on biopsy) or if the patient is refractory to agents aimed at stopping the bleeding. Low-dose combined oral contraceptives would regulate her bleeding but would not provide any information about the endometrium. Endometrial ablation would serve to provide symptomatic relief but would not generally be recommended in women thought to be at increased risk of hyperplasia or endometrial cancer. Biopsy is usually recommended before ablation is performed. Levonorgestrel IUD represents a good treatment option after biopsy of the endometrium.

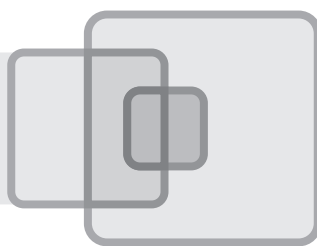
2. The answer is C [IV C 1]. Polycystic ovary syndrome is the classic condition that causes DUB due to estrogen breakthrough bleeding. Present in 5% to 10% of women of reproductive age, this condition involves a complex set of endocrine derangements, including anovulation. PCOS is also associated with hyperandrogenism, insulin resistance, and often obesity, each playing a role in the evolution of an oligo-ovulatory state. Increased endogenous estrogen associated with obesity likely contributes to her anovulatory state but there is no evidence to suggest that she is exposed to exogenous estrogen. Hyperandrogenism can also be seen in the presence of a testosterone-secreting tumor of the ovary or adrenal, but her long history of oligomenorrhea makes this less likely. A total serum testosterone greater than 200 ng/dL would suggest a testosterone-producing tumor of the ovary or adrenal. Thyroid dysfunction may also cause anovulation through dysregulation of a feedback loop that results in increased prolactin levels. Her long history including hyperandrogenism (acne and excess hair growth) and obesity, again make this diagnosis less likely. A similar bleeding pattern could be seen with progestin-only contraception such as DMPA or the "mini-pill," but such hormonally-related bleeding would be due to progesterone breakthrough rather than estrogen breakthrough as seen here. This patient desires pregnancy and is not exposed to exogenous progestin. Women with PCOS are at risk for cardiovascular illness and diabetes mellitus. They are also at increased risk for endometrial hyperplasia and endometrial cancer because of long-term unopposed estrogen stimulation of the endometrium.

3. The answer is E [V A 4]. von Willebrand disease and other bleeding disorders should be considered in the differential when evaluating patients with menorrhagia, especially when severe vaginal bleeding is experienced at the time of menarche. Although anovulatory uterine bleeding is common during early adolescence, the severity of symptoms in this patient warrants further investigation and therefore reassurance alone is not appropriate in this situation. Endometrial biopsy should be performed in any woman older than 35 years with abnormal uterine bleeding, or in any woman with a high risk of endometrial cancer. This young woman just recently experienced menarche and therefore does not have a long history of unopposed estrogen that would put her at increased risk. An endometrial biopsy would not be indicated for her at this time. NSAIDs have been shown to reduce menstrual flow by up to 50%; however, there is no role for this medication in the acute setting. As the majority of cases of abnormal uterine bleeding respond to hormonal manipulation, D&C with hysteroscopy would not be indicated as first-line treatment. A low-dose oral contraceptive given as three pills a day with taper over 3 to 4 days is an effective way to stop dysfunctional bleeding fairly quickly. Combined oral contraceptives are the first-line treatment for von Willebrand disease and menorrhagia.

4. The answer is B [IV D 2]. Progestin-only contraceptive methods and combined oral contraceptives alike rely on the progestin component to block ovulation in order to prevent pregnancy. The estrogen

component of combined oral contraceptives serves to add cycle control that is not present with progestin-only contraceptive methods such as the “mini-pill,” DMPA, or progestin implants. Although low-dose combined oral contraceptives contain estrogen and progestin, the effect is still predominantly progestational, and progesterone breakthrough bleeding occurs as the ratio of progesterone to estrogen is unfavorably high. The endometrial lining is most likely atrophic due to long-term effects of the progestin, and endometrial hyperplasia is unlikely given her long-term use of combined oral contraceptives. Estrogen breakthrough bleeding occurs when there is unopposed estrogen stimulation causing excess glandular proliferation that results in an unstable, thickened endometrium prone to irregular shedding. The possibility of pregnancy must be ruled out in anyone of reproductive age with abnormal uterine bleeding, even with contraceptive use. Low-dose combined oral contraceptives are highly effective in prevention of pregnancy but do carry a low failure rate even with perfect use. The timing and not the quantity of abnormal uterine bleeding is the issue and therefore it is unlikely that this represents a bleeding disorder.

5. The answer is D [V D 1]. Menstrual calendars can often clarify current bleeding history to help determine if anovulatory uterine bleeding is present and if endometrial biopsy is warranted. This woman very clearly has a history of regular cyclic menstrual flow, and so a menstrual calendar is unlikely to provide any additional information. Her cyclic bleeding pattern suggests that she does not have an ovulation disorder and that the bleeding is most likely from a structural problem. The test most likely to aid in diagnosis would be a pelvic ultrasound to look for the presence of fibroids, endometrial polyps, or adenomyosis. Transvaginal ultrasound is usually more sensitive than transabdominal ultrasound. Sonohysterogram, in which saline is instilled into the uterine cavity during transvaginal sonography, is a useful diagnostic test if pelvic ultrasound demonstrates a thickened lining that raises the suspicion of an intracavitary lesion. An endometrial biopsy is not warranted since the bleeding is regular and cyclic and there is no intermenstrual bleeding, making the diagnosis of endometrial hyperplasia or cancer unlikely. If a biopsy were performed in the latter half of the menstrual cycle, a finding of secretory endometrium would just confirm that this woman does not have an ovulation disorder. Office urine pregnancy tests are easy to perform and therefore usually done in any woman of reproductive age that presents with abnormal uterine bleeding. However, pregnancy is an unlikely diagnosis in a 46-year-old with a history of bilateral tubal ligation. TSH is a recommended test in any case of abnormal uterine bleeding where anovulatory bleeding is suspected. Extreme hypo- or hyperthyroidism can cause irregular menses and anovulation, but usually does not cause menorrhagia. It is unlikely that thyroid abnormalities would cause this regular but heavy menstrual flow.



Polycystic Ovary Syndrome

MARY E. RAUSCH • ANUJA DOKRAS

I

INTRODUCTION

First defined in 1935, Stein and Leventhal described a condition of obesity, amenorrhea or oligomenorrhea, bilateral polycystic ovaries, and “masculinizing changes.” More than 70 years later the etiology of this condition, now known as polycystic ovary syndrome (PCOS), still remains incompletely understood. PCOS is the most common endocrine abnormality of reproductive-aged women. The prevalence of PCOS is between 4% and 10% of reproductive-aged women. Using these statistics, there are an estimated 4 to 5 million women of reproductive age in the USA affected by PCOS.

II

DEFINITION

A Rotterdam criteria In 2003, American and European reproductive societies met in Rotterdam to determine a consensus about the diagnostic criteria for PCOS. The following criteria were put forth in an effort to standardize the diagnosis of PCOS. These criteria require two out of three of the following (ovulatory dysfunction, hyperandrogenism, or polycystic ovaries) to make a diagnosis in addition to exclusion of other causes of hyperandrogenism and oligomenorrhea (Table 24–1).

1. **Ovulatory dysfunction.** Most patients with PCOS have ovulatory dysfunction which is manifested as menstrual irregularities, such as oligomenorrhea (fewer than normal menses) or amenorrhea (no menses).
 - a. **Oligomenorrhea** is defined as 35 or more days between menses, or less than ten menses per year.
 - b. A total of 60% to 85% of patients with PCOS and oligo-ovulation will have oligomenorrhea, but the remainder may seemingly have normal menses. Therefore, presence of ovulation can be verified through alternative means, such as checking for an elevated progesterone level in the luteal phase of the cycle.
 - c. As a result of irregular ovulation, these women lack adequate progesterone and experience chronic estrogen exposure to the endometrium. This can result in breakthrough or irregular uterine bleeding and can put these patients at increased risk for endometrial hyperplasia and cancer.
2. **Hyperandrogenism.** Patients may either have clinical or biochemical hyperandrogenism.
 - a. **Clinical hyperandrogenism.** Women with PCOS may exhibit hirsutism, acne, or male pattern hair loss.
 - (1) Hirsutism is defined as excess pigmented hair in a male pattern distribution, most commonly found in midline areas of the body such as on the upper lip, chin, neck, chest, lower abdomen, and inner thighs. Male pattern baldness is also associated with hyperandrogenism.
 - (2) A formal scoring system, known as the Ferriman–Gallwey score, can be used to clinically estimate the extent of hirsutism and a score greater than or equal to 8 is considered abnormal.
 - (3) Acne maybe a more sensitive clinical sign of hyperandrogenism, especially in adolescents and those of Asian descent, who in general have less body hair.
 - (4) The rate of hair growth is also clinically important. PCOS is associated with slow but progressive hair growth. Rapid onset of hirsutism or acne suggests an ovarian or adrenal androgen-producing tumor or drug exposure. In addition, more severe signs of hyperandrogenism such as enlarging of the clitoris or deepening of the voice are rare with PCOS, and are more consistent with tumor or drug exposure.

TABLE 24–1 Differential Diagnosis for Polycystic Ovary Syndrome

Nonclassical adrenal hyperplasia
Cushing's syndrome
Androgen-producing tumor: adrenal, ovary
Thyroid disease
Hyperprolactinemia
Ovarian failure
Drug exposure
Hypothalamic amenorrhea

- b. Biochemical hyperandrogenism.** Up to 90% of women with PCOS have elevated serum androgen levels. However, the androgen levels may be normal even in the presence of clinical hyperandrogenism due to variability in current laboratory methods for measuring total and free testosterone levels as well as increased end organ sensitivity.
- (1) Typically, testosterone and free testosterone are measured and are usually in the upper range of normal or slightly above the normal range for women. High levels of testosterone (greater than 200 ng/dL) may suggest an ovarian or adrenal tumor.
 - (2) Dehydroepiandrosterone sulfate (DHEAS) is a marker of adrenal androgen production, and is slightly elevated in women with PCOS. DHEAS levels greater than 700 ng/dL suggest an adrenal tumor, but this is very rare.
- 3. Polycystic ovaries.** A diagnosis of polycystic-appearing ovaries can be made using pelvic ultrasound (Fig. 24–1).
- a.** PCO by ultrasound criteria is defined as either
 - (1) Twelve or more antral follicles between 2 and 9 mm in size (classically referred to as the “string of pearls sign” when follicles are located peripherally in the ovary, although follicle distribution is longer a diagnostic criteria).
 - (2) Increased ovarian volume (>10 mL) in one or both ovaries.
 - b.** Transvaginal ultrasound is more sensitive than a transabdominal approach, particularly in obese patients, but may not be appropriate to perform in a young female.
- 4. Exclusion of other causes of hyperandrogenism and menstrual irregularities**
- a.** Nonclassic adrenal hyperplasia
 - b.** Cushing's syndrome

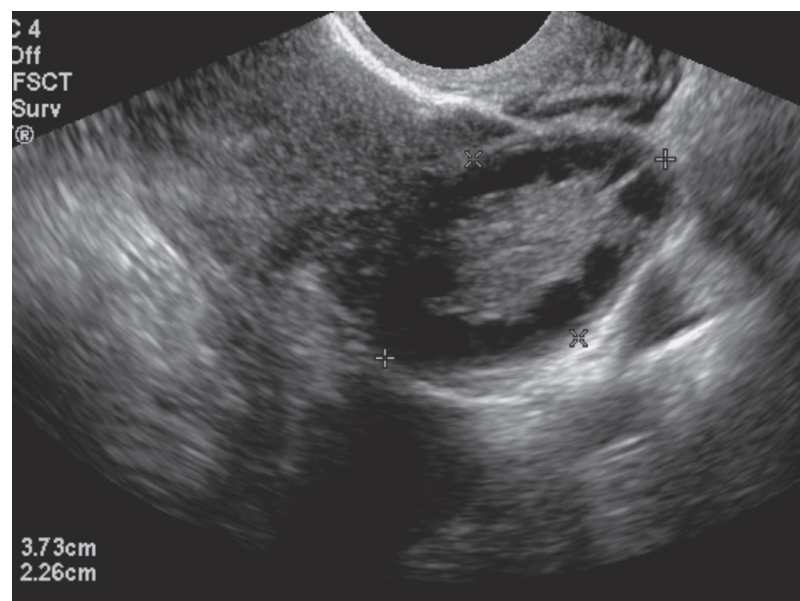


FIGURE 24–1 Transvaginal ultrasound showing characteristic polycystic appearance of the ovary. Multiple small dark circles line the periphery of the ovary.

- c. Androgen-producing tumor (ovarian and adrenal)
- d. Exogenous steroid hormones and drugs with hyperandrogenic effect
- e. Thyroid and prolactin disorders
- f. Premature ovarian failure
- g. Hypothalamic amenorrhea

III

GENETICS AND ETIOLOGY OF PCOS

PCOS is thought to have a multifactorial etiology. Although there is a genetic component, the manifestation of the syndrome is influenced by nonhereditary factors as well.

A Genetic studies Multiple studies have looked at the inheritance pattern of PCOS.

1. The prevalence of PCOS among first-degree relatives appears to be between 35% and 40%.
2. Among siblings of women with PCOS who do not meet the criteria for diagnosis, there appears to be increased rates of either isolated hyperandrogenemia or asymptomatic polycystic ovaries by imaging studies.
3. Insulin resistance among family members of patients with PCOS also appears to be significantly greater than that of the general population.

B Candidate genes

1. Although PCOS appears to have a genetic origin, at the present time, there is no known single responsible gene, and it is likely a complex genetic disorder.
2. Candidate genes that have been investigated include genes involved in androgen biosynthesis, secretion, transport, and metabolism, as well as genes involved in the insulin signaling pathway.

IV

PATHOPHYSIOLOGY

The development of the symptoms and signs of PCOS may be the result of one or more of several abnormalities ultimately leading to a state of hyperandrogenism. These include abnormal GnRH pulsatility, increased luteinizing hormone (LH) pulsatility, and hyperinsulinism secondary to insulin resistance.

A Increased luteinizing hormone

1. LH stimulates production of androgens from the theca cells in the ovary. Normally, androgens in the ovary are converted to estrogens in the granulosa cells. In women with PCOS, increased LH stimulation results in hyperandrogenism.
2. LH stimulation of androgens in women with PCOS may be due to
 - a. Elevated LH levels: Women with PCOS have been found to have increased LH pulse frequency and amplitude. It is unclear whether the abnormal GnRH secretion is a result of the lack of the feedback mechanism because of the low progesterone levels or an intrinsic defect in GnRH pulse generator
 - b. An overactive LH resulting from a polymorphism in the gene for the beta-subunit
 - c. Increased expression of LH receptor in theca cell

B Insulin resistance Insulin resistance is defined as a decreased ability of insulin to act on peripheral tissues to stimulate glucose metabolism or inhibit hepatic glucose output. This results in hyperinsulinemia. In PCOS, **insulin resistance is present in more than 50% women, independent of obesity**. Selective insulin resistance has been demonstrated in the liver, muscle, and adipose tissue affecting glucose transport and metabolic actions. The resulting hyperinsulinemia continues to stimulate ovarian steroidogenesis and **increases production of androgens**. Proposed mechanisms include:

1. Insulin directly stimulates production of androgens from theca cells by binding to its receptor.
2. Insulin has been shown to work synergistically with LH to increase theca cell androgen production, possibly through insulin receptors or insulin-like growth factors (IGF) receptors on the cells.

3. Insulin also decreases the production of sex hormone-binding globulin (SHBG) produced by the liver. This in turn decreases the amount of testosterone bound to SHBG and therefore increases the free metabolically active testosterone.
4. The theca cells of women with PCOS may also be more sensitive to stimulation by insulin and more efficient in converting androgenic precursors to testosterone, resulting in enhanced steroid production.

V**HEALTH CONSEQUENCES**

PCOS is a metabolic disorder and is associated with other medical conditions. Identifying the patient with PCOS is important so that these comorbidities can be screened and ideally prevented.

A Diabetes

1. In studies of women with PCOS, the prevalence of diabetes has been shown to be as high as 2% to 10% demonstrating a 3- to 7-fold increased risk compared to age and weight matched controls.
2. Impaired glucose tolerance diagnosed by a 2-hour glucose tolerance test is seen in up to 35% of women with PCOS. Impaired glucose tolerance is considered a precursor to diabetes and therefore, if treated, can prevent the development of diabetes.

B Obesity

1. Obesity has been reported in 30% to 70% of all patients with PCOS. The obesity is most often truncal with an android appearance and an increased waist-to-hip ratio.
2. Obesity is related to insulin resistance. The incidence of insulin resistance in women with PCOS has been demonstrated to be as high as 60%.

C Cardiovascular disease There is increasing evidence to suggest that women with PCOS have an increased risk for cardiovascular disease. This is related to an increased risk for hypertension, dyslipidemia, and glucose abnormalities. Metabolic syndrome is a constellation of cardiovascular disease risk factors associated with insulin resistance. Criteria include elevated blood pressure (BP), increased waist circumference, elevated fasting glucose levels, an elevated triglyceride level, and a reduced high-density lipoprotein (HDL) cholesterol level. This syndrome is seen in a high proportion of women with PCOS (20% to 40%).

D Endometrial hyperplasia Chronic anovulation exposes the endometrium to unopposed estrogen, which puts women with PCOS at risk for endometrial hyperplasia. If left untreated, endometrial hyperplasia may progress to endometrial cancer.

E Infertility Infertility is associated with PCOS. The cause of the infertility in these women is primarily anovulation.

VI**DIFFERENTIAL DIAGNOSIS**

In order to make a diagnosis of PCOS, other causes of ovulatory disorders and hyperandrogenism must be excluded.

A Nonclassical adrenal hyperplasia (NCAH)

1. Women with NCAH, also known as late-onset adrenal hyperplasia, present with anovulation, hirsutism, and infertility similarly to women with PCOS. The constellation of symptoms is due to an enzymatic defect which disrupts the normal pathway converting cholesterol to sex steroids and mineralocorticoids. The most common enzymatic defect in NCAH is 21-hydroxylase deficiency; the lesser two are 3 β -hydroxysteroid dehydrogenase deficiency and 11 β -hydroxylase deficiency.
2. 21-Hydroxylase deficiency is an autosomal recessive disorder. The gene is located on chromosome 6. It is most common in those of Eastern European Jewish, Hispanic, Slavic, and Italian descent.
3. The deficiency in 21-hydroxylase enzyme leads to accumulation of the precursor 17-hydroxy progesterone (17-OHP) in the adrenal gland. This in turn results in elevated production of androstenedione and testosterone.

4. The diagnosis is made by measuring the 17-OHP level at 8 AM in the follicular phase of the menstrual cycle, with a confirmatory adrenocorticotrophic hormone (ACTH) stimulation test if the 17-OHP levels are greater than 2 ng/mL.

B Cushing's syndrome

1. The findings in Cushing's syndrome can resemble those of PCOS and include obesity, hypertension, abdominal striae, hirsutism, acne, and menstrual irregularities.
2. These findings result from excess cortisol production, either from an adrenal neoplasm, excess ACTH from a pituitary tumor, or an ectopic source of ACTH.
3. Only women with late onset of PCOS or who have stigmata of Cushing's syndrome should be tested as the condition is relatively uncommon. Diagnosis is made by 24-hour urinary collection to measure free cortisol or a low-dose dexamethasone suppression test.

C Androgen-producing neoplasm Early stages of androgen-producing tumors can resemble PCOS and should be considered in cases in which there is a more rapid onset of hirsutism or signs of virilization. The location of the neoplasm could be either the adrenal gland or the ovary. Common ovarian tumors include Sertoli–Leydig cell, granulosa cell, fibroma, thecoma, and luteoma of pregnancy.

D Ovarian hyperthecosis Ovarian hyperthecosis is a condition of the ovary where nests of luteinized theca cells are present in the ovarian stroma. These patients have elevated serum androgen levels and therefore demonstrate hirsutism, and in fact often show signs of virilization.

E Hyperandrogenic drugs Drug exposure can lead to a rapid onset of hyperandrogenic symptoms, usually over several months. Implicated drugs include anabolic steroids, methyltestosterone, phenytoin, danazol, cyclosporin, and minoxidil.

F Premature ovarian failure presents with menstrual irregularity. Typical symptoms include hot flashes and night sweats. Diagnosis is made by elevated follicle-stimulating hormone (FSH) and low estradiol in the setting of amenorrhea.

G Hypothalamic amenorrhea is another cause of menstrual irregularity, and is often associated with stress, eating disorders, and excessive exercise. Laboratory evaluation in these women includes documenting low levels of FSH and LH.

H Severe extremes of **hypothyroidism** or **hyperthyroidism** can also lead to menstrual irregularity.

I Hyperprolactinemia results in hypothalamic suppression and amenorrhea. It can also be associated with hirsutism.

VII EVALUATION

The diagnosis of PCOS can often be suspected by history and physical examination alone. However, laboratory evaluation is important to exclude other causes of the symptoms prior to confirming the diagnosis of PCOS.

A History

1. **Menstrual cycle frequency and duration:** Menstrual irregularity (oligomenorrhea or amenorrhea) is indicative of oligo-ovulation or anovulation
 - a. **Oligomenorrhea** is defined as menses occurring at intervals of 35 days or greater than 35 days, or less than 10 menses per year
 - b. **Amenorrhea** is defined as no menses
2. **Onset and duration of hirsutism and acne**
 - a. With PCOS, symptoms start with the onset of puberty and are slowly progressive. The rate and degree of hirsutism is variable among individuals. It is important to ask the patient if she has excessive hair growth and methods used to remove unwanted hair.
 - b. An androgen-producing tumor or drug exposure will be associated with a rapid progression of hirsutism, acne, and virilization.
3. **Family history** of diabetes and cardiovascular disease

B Physical findings**1. Hirsutism**

- a. Excess male pattern hair growth seen primarily in areas such as the face, jaw, chin, neck, midline on chest and abdomen, and inner thighs.
- b. Racial and ethnic differences exist; for example, Asian individuals usually do not have much body hair and therefore may not display significant hirsutism even if elevated androgen levels are present.
- c. The **Ferriman–Gallwey scoring system** is used to quantify the amount of hair growth. Each area of the body is scored for the amount of hair. A score of greater than or equal to 8 is considered hirsute.

2. Acne

- a. May be a more reliable clinical marker of hyperandrogenism than hirsutism in adolescents and ethnic groups without significant hair growth in general (i.e., Asians); however, there is currently no standardized scoring system.
- b. Usually involves the face, chest, and back beyond the teenage years.

3. Signs of insulin resistance

- a. **Acanthosis nigricans:** Raised, velvety, hyperpigmentation of skin, typically seen on the axilla, neck, and intertriginous areas.
- b. **Hypertension:** BP must be checked at every visit.

4. Obesity

- a. Defined as a body mass index (BMI) greater than or equal to 30 kg/m²
- b. Incidence of obesity in women with PCOS is as high as 80% in the USA
- c. Central obesity with an increased waist-to-hip ratio (“apple” versus “pear”)

C Laboratory testing**1. Making the diagnosis:** Documentation of biochemical hyperandrogenemia and exclusion of other causes of hyperandrogenism or anovulation**a. Total and free testosterone**

- (1) Hyperandrogenemia may be documented via elevation in either total or free testosterone. Free testosterone concentration may be measured directly (by equilibrium dialysis) or calculated on the basis of the total testosterone and SHBG.
- (2) Total testosterone greater than 200 ng/dL is suggestive of an androgen-producing tumor. Imaging of the ovaries and adrenals is indicated.

b. Thyroid-stimulating hormone (TSH) and prolactin to exclude thyroid dysfunction and hyperprolactinemia. Prolactin may be elevated in up to 40% of patients with PCOS, but this is likely secondary to stimulation of the prolactin-producing cells by chronic estrogen and not related to the cause of the disease state.**c. FSH and estradiol to exclude the possibility of premature ovarian failure in those women with oligomenorrhea or amenorrhea.**

- (1) FSH greater than 40 pg/mL
- (2) Associated with a suppressed estradiol less than 30 pg/mL
- (3) Measuring LH and FSH to assess the LH-to-FSH ratio is not recommended. Although a ratio of greater than 2 is associated with PCOS, it is only present in approximately 40% of individuals and is not considered diagnostic for PCOS

d. 17-Hydroxyprogesterone to rule out NCAH. It is important to draw this blood sample at a specific time:

- (1) Early in the morning (i.e., 8 AM), due to the diurnal variation of hormone secretion from the adrenal gland. The peak is in the early morning; the lowest production is in the late afternoon.
- (2) In the follicular phase of the menstrual cycle. After ovulation the ovary produces 17-hydroxyprogesterone so the level would reflect secretion from both the ovary and adrenal gland and therefore not reflect just adrenal production.

e. Increased production of cortisol is associated with Cushing’s syndrome. Laboratory evaluation is reserved for cases where there is a clinical suspicion for the disease. Diagnosis is made by:

- (1) 1-mg overnight dexamethasone suppression test
- (2) 24-hour urinary-free cortisol excretion elevated on two separate collections

TABLE 24–2 Two-Hour Oral Glucose Tolerance Test*

	Fasting Serum Glucose (mg/dL)	2-hr Serum Glucose (mg/dL)
Normal	<100	<140
Impaired glucose tolerance	100–125	140–199
Diabetes	≥126	≥200

*Fasting serum glucose is drawn, then a 75-g oral glucose load is given, and then serum glucose is drawn 2 hours later.

- f. DHEAS level greater than 700 ng/mL is suggestive of an adrenal tumor and warrants imaging of the adrenals.
 - (1) Moderately elevated DHEAS levels may occur with anovulation, PCOS, or adrenal hyperplasia.
 - (2) Normal DHEAS levels indicate that adrenal disease is less probable and that ovarian androgen production is more likely.
 - (3) Measuring DHEAS is not necessary unless an androgen-producing tumor is suspected. A mildly elevated level is nonspecific and does not help in making a diagnosis or determining treatment.
2. **Other testing that should be done once the diagnosis of PCOS is established**
 - a. **Insulin resistance.** There is no recommended screening test for insulin resistance. The most accurate testing is the euglycemic clamp technique or the frequently sampled IV glucose tolerance test. However, both of these tests require inpatient monitoring and are therefore best suited for research protocols and not for outpatient screening. Instead, women can be assessed for metabolic syndrome, which is a clinical phenotype of insulin resistance.
 - b. **Diabetes.** Since the incidence of diabetes in women with PCOS is 2% to 10% and impaired glucose tolerance is seen in up to 40% of women, it is important to screen for these conditions as treatment can prevent significant health problems. Further, even women with PCOS who have normal glucose tolerance are at risk for converting to impaired glucose tolerance (estimates range from 9% in 6 years to 16% per year), and therefore need to be rescreened every other year.
 - (1) **Two-hour glucose tolerance test** is the best test to evaluate for these conditions in women with PCOS. This test involves measuring fasting level of glucose, then administering an oral 75-g glucose load, then drawing glucose level at 2-hours (Table 24–2).
 - (2) A fasting glucose level alone will miss a high proportion of diabetes in PCOS women.
 - c. **Fasting lipid and lipoprotein levels.** Although not involved in the clinical diagnosis of PCOS, abnormal lipid profiles are common in PCOS patients.
 - (1) Studies have shown that patients with PCOS have elevated triglycerides and low high-density lipoprotein (HDL) concentrations even relative to weight-matched controls.
 - (2) These abnormalities predispose to vascular and cardiac disease, and therefore measurement and treatment of serum lipid levels is recommended every other year to decrease the risk of cardiovascular disease.

VIII TREATMENT

Treatment of PCOS involves treating each manifestations of the disorder.

- A Menstrual irregularity** Prolonged unopposed estrogen exposure and amenorrhea can lead to endometrial hyperplasia and endometrial cancer.
 1. In patients who have had prolonged anovulation without treatment or have had a history of oligomenorrhea, an endometrial biopsy is indicated in order to rule out endometrial hyperplasia and/or cancer.
 2. Treatment with progestin is important to prevent hyperplasia and regulate menstrual bleeding.
 - a. Combined hormonal contraception: oral contraceptive pills
 - b. Only progestin therapy, either cyclic oral progestin therapy, administered 12 days a month, implant, or progestin-containing intrauterine device, is an alternative.

B Treatment of hirsutism**1. Mechanical removal of hair**

- a. Shaving, plucking, bleaching, depilation
- b. Electrolysis achieves permanent hair removal. If done incorrectly, it may be associated with scarring
- c. Laser epilation is most effective and now available for women of most skin colors
- d. Eflornithine HCl (Vaniqa) cream which inhibits enzyme ornithine decarboxylase, acts directly at the hair follicle, and slows facial hair growth

2. Combined hormonal contraception. Combined contraception with estrogen and progestin works to treat hyperandrogenism by the following mechanisms:

- a. Decreases androgen production through suppression of LH and therefore suppresses androgen production by the ovarian theca cells
- b. Increases production of SHBG, which in turn decreases free circulating androgens
- c. May decrease androgen secretion by the adrenal gland
- d. Less androgenic progestins are preferred however, the best hormonal contraceptive is the one that is best tolerated by the individual

3. Antiandrogens work to suppress hirsutism by competitive inhibition at the level of the testosterone receptor. Several antiandrogens have been used successfully to treat hirsutism. Improved results are seen when these agents are used with hormonal contraceptives which will also minimize the risk of conception when taking anti-androgens.

- a. Spironolactone (25 to 100 mg twice daily): aldosterone antagonist; and the clinical effect may take several months and may induce hyperkalemia
- b. Flutamide (125 to 250 mg/d): androgen-receptor agonist; rare association with hepatotoxicity
- c. Finasteride (5 mg/d): 5 α -reductase inhibitor
- d. Cyproterone acetate: not available in the USA

C Metabolic correction Since the underlying condition in PCOS is insulin resistance, treating insulin resistance via weight loss or by insulin-sensitizing agents has been shown to result in improvement in PCOS symptoms.**1. Weight loss: Obesity** is associated with worsening of PCOS symptoms including menstrual irregularity, insulin resistance, risk of diabetes, and hyperandrogenic symptoms.

- a. Weight reduction results in improvement in all symptoms of obese women with PCOS. Approximately 5% of weight loss can result in improvement in menstrual cyclicity and fertility.
- b. Dietary composition of the diet has no impact on weight loss or menstrual cyclicity. Although a low-carbohydrate diet may be more effective since it leads to decreased insulin secretion, studies have shown that both low-carbohydrate and low-fat diets are equally effective. Calorie restriction is the most important factor and should be combined with an exercise regimen.
- c. Bariatric surgery may be another modality for treatment of obesity in individuals with BMIs greater than or equal to 40 kg/m², or BMIs greater than or equal to 35 kg/m² if significant health problems exist. Weight loss of 20 to 40 kg is maintained for up to 10 years.

2. Metformin is a biguanide that acts by decreasing hepatic glucose production and may also increase peripheral glucose utilization. It is primarily used to prevent the progression of impaired glucose tolerance (IGT) and for the treatment of diabetes. Women with PCOS metformin can

- a. Improve menstrual cyclicity and ovulation rates
- b. May decrease serum androgens but the effect on hirsutism is unclear
- c. Improve insulin resistance
- d. Weight loss with metformin occurs only in conjunction with a low-calorie diet and exercise regimen
- e. Side effects are primarily gastrointestinal, including nausea and diarrhea

3. Thiazolidinediones. These insulin sensitizers have been shown to improve androgens and insulin resistance and include rosiglitazone and pioglitazone. However, these medications have been associated with hepatotoxicity, which has limited their use in PCOS. They are approved for the treatment of diabetes.

D Treatment of infertility Women with PCOS often have difficulty conceiving because of the failure to ovulate regularly. The use of ovulation induction agents has been shown to be effective.

1. Clomiphene citrate is an antiestrogen that has been used since the 1960s to induce ovulation, and is the first-line treatment for anovulatory infertility. A total of 40% to 60% of women will have a live birth after 6 months of treatment.
2. Metformin is associated with an improvement in ovulation. Recent studies have shown clomiphene to be more successful in achieving ovulation and pregnancy compared to metformin alone. However, in those who do not respond to clomiphene alone, the addition of metformin may improve ovulation rates in some individuals.
3. Gonadotropins, FSH alone or in combination with LH, is successful in inducing ovulation. However, the risks include high-order multiple gestation and hyperstimulation, and are usually reserved for women who fail clomiphene therapy.
4. Laparoscopic ovarian drilling (with laser or diathermy) is another second-line option for fertility.
5. Aromatase inhibitors, such as letrozole and anastrozole, are currently being studied for use to induce ovulation in women with PCOS.
6. In vitro fertilization is successful in achieving pregnancy and ovulation in women with PCOS, but is a more aggressive therapy than the previous options.



Study Questions for Chapter 24

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A 30-year-old woman presents to your office with an ultrasound report stating she has “polycystic-appearing ovaries.” She has a friend who has PCOS and is currently having trouble conceiving and wants to know what this means for her. You tell her that she may have PCOS if she also

- ☐ A Occasionally skips a menstrual cycle
- ☐ B Is obese
- ☐ C Is hirsute
- ☐ D Has diabetes
- ☐ E Has elevated LH levels

2. A 25-year-old woman comes to your office complaining of irregular menses and hair on her chin, upper lip, and chest that requires frequent plucking. She reports that she is otherwise healthy. On physical examination, you notice increased hair on her lower abdomen and upper back, but the rest of the examination and her vitals are normal. Which laboratory tests would you NOT order for this patient?

- ☐ A Serum testosterone
- ☐ B Prolactin
- ☐ C 17-OHP
- ☐ D 24-hour urinary free cortisol
- ☐ E FSH and estradiol level

3. You diagnose the previous patient with PCOS and she would like to know what she can do to help with the excessive hair growth. She is currently on no medications. Which one of the following treatments for hirsutism would you NOT prescribe to her alone?

- ☐ A Metformin
- ☐ B Flutamide
- ☐ C Laser epilation
- ☐ D Oral contraceptive pills
- ☐ E Eflornithine

4. A 36-year-old obese woman with known PCOS presents to your infertility practice. She was diagnosed with PCOS at the age of 24 years, at which time she reports having had a battery of tests done. She has been followed by her general gynecologist who has maintained her on oral contraceptive pills since that time. She reports she is otherwise healthy. She now desires to get pregnant and is coming to you for advice. What is one of the most important tests to perform at this time?

- ☐ A Ovarian ultrasound
- ☐ B Endometrial biopsy
- ☐ C Serum testosterone
- ☐ D Fasting glucose levels
- ☐ E 2-hour oral glucose tolerance test

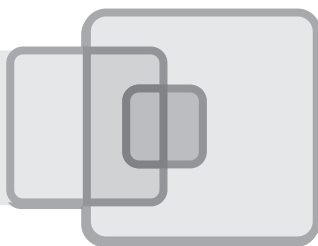
5. A 28-year-old women with PCOS and her husband present to your infertility clinic for consultation. She stopped taking her oral contraceptive pills 6 months ago and has not had a period since. She is morbidly obese and her past medical history is significant for sleep apnea and diabetes. She and her husband want get pregnant and ask for your help. What would be your first recommendation to increase their chances of conception at this time?

- ☐ A In vitro fertilization
- ☐ B Clomiphene citrate
- ☐ C Gonadotropins
- ☐ D Weight loss program
- ☐ E Metformin



Answers and Explanations

1. **The answer is C** [II A]. According to the Rotterdam criteria, PCOS is diagnosed when a patient has two of the following three criteria (ovulatory dysfunction, hyperandrogenism, or polycystic ovaries) in addition to ruling out other causes for her symptoms. This patient has polycystic ovaries on ultrasound, but only answer C *is hirsute* fulfills the criteria for hyperandrogenism. Occasionally skipping a menstrual cycle does not fulfill the definition of amenorrhea or oligomenorrhea. Amenorrhea is lack of menses and oligomenorrhea is defined as 35 or more days between menses, or less than ten menses per year. Obesity, diabetes, and elevated LH levels are all associated with PCOS, but are not diagnostic.
2. **The answer is D** [VII C 1]. Work-up for a patient with oligomenorrhea and clinical signs of hyperandrogenism should involve evaluation for biochemical hyperandrogenism, as well as for other causes for her symptoms. In a patient with irregular menses, prolactin should be checked, and an FSH with estradiol can assist in diagnosing premature ovarian failure. The serum testosterone may be elevated in this patient, but levels greater than 200 ng/dL suggest an androgen-producing neoplasm and therefore would require further investigation. Similarly, an elevated 17-OH progesterone level will diagnose 21-hydroxylase deficiency, the most common cause of congenital adrenal hyperplasia, which can mimic PCOS. A 24-hour urinary free cortisol would be a diagnostic test for Cushing's disease. This test would only be done if she presented with late-onset PCOS or had stigmata of Cushing's syndrome (obesity, hypertension, abdominal striae, hirsutism, acne, and menstrual irregularities). Since this patient does not, the test is not indicated.
3. **The answer is B** [VIII B 3]. Flutamide is teratogenic and should not be prescribed to a woman in her reproductive years without ensuring she had proper contraception, usually in the form of combined hormonal contraception which will also treat the hirsutism.
4. **The answer is E** [VII C 2 b]. This patient has a long history of PCOS and is obese, and even though she may have been tested for glucose tolerance years ago, women with PCOS are at increased risk for conversion to impaired glucose tolerance per year, and therefore need to be rescreened periodically. The 2-hour glucose tolerance test is the best test to evaluate for these conditions in women with PCOS. A fasting glucose is a poor predictor of glucose intolerance risk in PCOS women. Serum testosterone and ovarian ultrasound are used for the diagnosis of PCOS, and this woman already carries an established diagnosis. Given that she has been on oral contraceptive pills for endometrial protection, an endometrial biopsy is not warranted at this time.
5. **The answer is D** [VIII C 1]. Obesity compounds the effects of PCOS, including menstrual irregularity, insulin resistance, and hirsutism, and causes problems during pregnancy for both the mother (higher risk of diabetes, hypertension, and need for cesarean section) and the baby (higher risk of fetal distress). Given this patient's morbid obesity with concurrent diabetes and sleep apnea, weight loss is the most prudent measure at this time. Her treatment may include lifestyle modifications, medication, and surgery. Given her young age and the severity of her obesity and medical comorbidities, immediate treatment with any infertility medications would not be the best first option.



Hirsutism and Other Hyperandrogenic Disorders

SARA PITTENGER • SAMANTHA M. PFEIFER

I

INTRODUCTION

Increased hair growth in women may be associated with normal or increased levels of **circulating androgens**. It is important to view hirsutism as a potential endocrine abnormality as well as a psychological and cosmetic problem.

A Definitions

1. Types of hair

- a. **Lanugo** is soft, short hair covering the fetus that is shed in late gestation and during the neonatal period.
- b. **Vellus** is soft, fine, unpigmented hair that covers apparently hairless areas of the body.
- c. **Terminal** is longer, coarse, pigmented hair that may grow in response to sex hormones (e.g., over the chin and abdomen of men) or may be sex hormone independent (e.g., eyebrows and eyelashes).

2. **Hypertrichosis** is excessive growth of androgen-independent hair in nonsexual areas, such as forearms and legs.

3. **Hirsutism** is the presence of terminal hair in androgen-dependent sites where hair does not normally grow in women. This hair growth is located predominantly on midline portions of the body, including the face, chest, abdomen, and inner thighs.

4. **Virilization** includes signs associated with hyperandrogenism, such as increased muscle mass, clitoromegaly, temporal balding, voice deepening, and increased libido. It can also be associated with signs of defeminization, such as decreased breast size and loss of vaginal lubrication. Virilization is associated with higher levels of androgens and should prompt evaluation for exogenous androgens or an androgen-producing tumor.

II

HAIR PHYSIOLOGY

From birth, vellus hair covers most of the human body. Terminal or androgenic hair appears after puberty as circulating androgens transform vellus hair follicles into terminal follicles in specific areas of the body. All hair goes through three growth cycles: anagen or growth phase, the catagen or transitional, and telogen or resting phase where hair is typically shed. Compared to hair on the scalp, body hair has a shorter anagen and longer telogen phase.

A Hair growth is regulated by:

1. **Number and concentration of hair follicles.** This varies according to racial and ethnic background but not gender. For example, Asian women generally have low concentrations of hair follicles, and hirsutism is rarely seen in these individuals
2. Degree to which hair follicles are sensitive to androgens and able to convert vellus hairs to terminal hairs
3. **Degree of 5 α -reductase activity** in the skin, which determines local androgen activity

4. Ratio of growth to resting phases in affected hair follicles
5. Thickness and degree to which individual hairs are pigmented

III

ANDROGENS

These steroids promote the development of male secondary sexual characteristics. In women, androgens are mainly produced by the adrenal gland, the ovary, and peripheral transformation. Testosterone is the most potent androgen; androstenedione, dehydroepiandrosterone (DHEA), and DHEA sulfate (DHEAS) are less potent.

A Testosterone Blood testosterone levels are a function of production rates and metabolic clearance rates; thus, these levels may not represent the actual state of androgenicity.

1. **Total testosterone** levels in women are usually less than 70 ng/dL.
2. **Sources:**
 - a. Ovarian: 25% (in stroma and follicles)
 - b. Adrenal origin: 25%
 - c. Peripheral transformation of androstenedione to testosterone: 50%
3. **Free testosterone**
 - a. Most testosterone in the blood circulates bound to **albumin** (19%) or to **sex hormone-binding globulin (SHBG; 80%)**. Percentages of free testosterone are as follows:
 - (1) Normal women: 1%
 - (2) Hirsute women: 2%
 - (3) Men: 2% to 3%
 - b. Androgenicity depends mainly on the unbound fraction of testosterone because this represents the active form of the hormone.

B Sex hormone-binding globulin

1. An inverse relationship exists between SHBG and the percentage of free testosterone. As SHBG decreases, the percentage of free testosterone increases; as SHBG increases, the percentage of free testosterone decreases. However, the total testosterone level may remain normal.
 - a. **Factors that decrease plasma SHBG**
 - (1) Obesity
 - (2) Increased androgen production
 - (3) Hyperinsulinemia
 - (4) Corticosteroid therapy
 - (5) Hypothyroidism
 - (6) Acromegaly
 - b. **Factors that increase plasma SHBG**
 - (1) Estrogen therapy
 - (2) Combined hormonal contraceptives
 - (3) Pregnancy
 - (4) Hyperthyroidism
 - (5) Cirrhosis
2. In general, hirsute women have reduced serum concentrations of SHBG and therefore elevated levels of free androgens.

C 5 α -Reductase

1. 5 α -Reductase converts testosterone to **dihydrotestosterone (DHT)** in androgen-sensitive tissues such as hair follicles and skin. Levels of this enzyme are significantly elevated in the skin of hirsute women compared with control subjects. The enzyme activity is partly stimulated by elevated circulating testosterone levels.
2. Dihydrotestosterone is responsible for stimulating hair growth and is two to three times as potent as testosterone.
3. **3 α -Androstenediol glucuronide (3 α -AG)** is the peripheral tissue metabolite of DHT. Although it has been used as a marker of target tissue cellular action, it is not often used clinically.

D Pathophysiology of androgens in hirsutism A combination of the following factors results in hirsutism:

1. Increased concentration of serum androgens, especially free testosterone
2. Decreased levels of SHBG, resulting in increased bioavailable androgen
3. Increased activity of 5 α -reductase in hair follicles

IV

DIAGNOSIS

A Differential diagnosis

1. **Polycystic ovary syndrome (PCOS)** (see Chapter 24). This heterogeneous endocrine, metabolic, and genetic disorder is seen in 5% to 10% of the general population and is the cause of androgen excess in 65% to 85% of hirsute patients. This syndrome is characterized by hyperandrogenism, oligomenorrhea, or amenorrhea (caused by chronic anovulation). It is associated with insulin resistance. Patients usually present with hirsutism, menstrual irregularity, and infertility.
 - a. The fundamental pathophysiologic defect is not known.
 - b. Increased production of androgens may result in:
 - (1) Increased secretion of luteinizing hormone (LH) from the anterior pituitary, leading to increased ovarian androgen production
 - (2) Insulin resistance and compensatory hyperinsulinemia, stimulating ovarian and adrenal androgen production by direct and indirect mechanisms
 - c. Gonadotropin regulation of the menstrual cycle is disrupted, leading to oligo-ovulation or anovulation and menstrual irregularity.
 - d. Increased androgen levels inhibit follicular development in the ovary; thus, multiple small atretic follicles are produced. These “polycystic ovaries” are therefore a reflection of the hormonal environment within the ovary rather than the cause of the disorder.
 - e. Affected patients are at increased risk for obesity, endometrial hyperplasia or cancer, glucose intolerance, type 2 diabetes mellitus, hyperlipidemia, and cardiovascular disease.
2. **Nonclassic adrenal hyperplasia (NCAH)**. This condition is present in approximately 1% of hyperandrogenic women. This is a less severe form of congenital adrenal hyperplasia that is diagnosed in the newborn. Patients present at or before puberty with acne, hirsutism, oligo- or amenorrhea, similar to those with PCOS. NCAH is not associated with ambiguous genitalia and salt wasting.
 - a. **Deficiency in activity of adrenal enzymes** and thus formation of excess cortisol precursors (e.g., 17-hydroxyprogesterone [17-OHP] and androstenedione) leads to increased production of androgens. The most common enzyme deficiency is 21-hydroxylase.
 - b. Inheritance is autosomal recessive, and occurrence is increased in Ashkenazi Jews.
 - c. Deficiencies of adrenal enzymes 11 β -hydroxylase and 3 β -hydroxysteroid dehydrogenase are less common.
3. **Cushing’s syndrome**
 - a. **Adrenocortical hyperfunction** leads to excess production of corticosteroids as well as hyperandrogenism, menstrual irregularities, glucose intolerance, and obesity.
 - b. Causes are multiple and include adrenal neoplasm, ectopic adrenocorticotrophic hormone (ACTH)-producing tumor, and pituitary tumor or Cushing’s disease.
4. **Androgen-producing tumors** are associated with sudden-onset hyperandrogenic state, rapid progression, and frank virilization.
 - a. **Ovarian tumors** (e.g., Sertoli–Leydig cell tumor, granulosa–theca cell tumor, thecoma, luteoma of pregnancy)
 - b. **Adrenal tumors**
5. **Pituitary disorders**
 - a. Hyperprolactinemia
 - b. Acromegaly
6. **Androgenic drug exposure**
 - a. **Without virilization:** phenytoin, diazoxide, minoxidil, danazol, corticosteroids, or cyclosporin
 - b. **With potential virilization:** anabolic steroids, androgen therapy, or supplements

7. **Y-containing mosaics** and **incomplete androgen insensitivity**. These patients show signs of androgen stimulation at puberty and may have ambiguous genitalia.
8. **Idiopathic hirsutism**. This condition, which accounts for 15% to 30% of hirsute women, is caused by end-organ (skin) hypersensitivity to androgens. Characteristics include:
 - a. Regular ovulatory menstrual cycles
 - b. Normal circulating androgen levels
 - c. Increased peripheral conversion of androgens caused by **increased skin 5 α -reductase activity**

B History Several factors are important.

1. **Onset of hirsutism**
 - a. **Gradual onset** of hirsutism is associated with acne, oily skin, weight gain, and irregular menstrual cycles. This suggests an underlying endocrine condition, such as PCOS.
 - b. **Abrupt onset** or rapidly worsening hirsutism with signs of virilization should prompt concern for an androgen-producing tumor.
2. Presence or absence of **virilization**.
3. **Drug ingestion**. Drugs are usually associated with hypertrichosis, but androgenic drugs (e.g., steroids and phenytoin) may cause hirsutism.
4. **Family history**. A family history of hirsutism may indicate an inherited disorder (i.e., familial hypertrichosis).
5. **Ethnic background**. The pattern of hair growth is genetically predetermined and is associated with differences in 5 α -reductase activity at hair follicles.
6. **Local trauma**. Changes in skin and hair growth may occur.
7. **Regularity of menstrual cycles**. Patients with regular menstrual cycles and hirsutism often have idiopathic, ethnic, or familial hirsutism. Hyperandrogenic disorders are usually associated with irregular or absent menstrual cycles.

C Laboratory evaluation

1. **Serum testosterone** (see III A) is a marker of ovarian and adrenal activity.
 - a. **Total testosterone levels greater than 200 ng/dL** suggest an androgen-producing tumor. However, 10% to 20% of patients with androgen-producing tumors may have low testosterone levels. Imaging is warranted.
 - (1) **Pelvic ultrasound or magnetic resonance imaging (MRI)** is best to provide an image of the ovaries.
 - (2) **Computed tomography or MRI** views the adrenal glands.
 - b. **Elevated total testosterone levels but less than 200 ng/dL** associated with anovulation and hirsutism suggest PCOS.
 - c. Testosterone may be in the normal range when measured in patients with PCOS.
2. **Serum DHEAS** is almost exclusively produced by the adrenal glands and reflects adrenal androgen activity.
 - a. Levels greater than 700 μ g/dL suggest an adrenal tumor.
 - b. Moderately elevated DHEAS levels may occur with anovulation, PCOS, or adrenal hyperplasia.
 - c. Normal DHEAS levels indicate that adrenal disease is less probable and that ovarian androgen production is more likely.
3. Elevated levels of **serum androstenedione** suggest ovarian disease, but this test is rarely recommended.
4. **Serum 17-hydroxy progesterone (17-OHP)**
 - a. 17-OHP is elevated in 21-hydroxylase deficiency, the most common form of NCAH. Normal values should be less than 200 ng/dL.
 - b. Circumstances under which 17-OHP must be measured:
 - (1) Early in the morning because of diurnal variation of adrenal secretion
 - (2) In the follicular phase of the menstrual cycle in ovulatory women to avoid confusion with ovarian production of this hormone in the luteal phase
 - c. Baseline values greater than 200 ng/dL are abnormal and should be further evaluated with the ACTH stimulation test to confirm the diagnosis of NCAH.

5. Increased production of **cortisol** is associated with Cushing's syndrome. Diagnosis is made by:
 - a. 1-mg overnight dexamethasone suppression test
 - b. 24-hour urinary-free cortisol excretion
6. **Gonadotropins** may be useful. An elevated LH-to-follicle-stimulating hormone (FSH) ratio (2 to 3:1) suggests PCOS. However, this finding is not present in approximately 40% of patients with PCOS and is not considered diagnostic.
7. **Serum 3 α -AG** is rarely measured. Increased levels of 3 α -AG indicate an increased activity of 5 α -reductase in the periphery and measure peripheral target tissue activity.
8. The evaluation of irregular menstrual cycles and hirsutism also includes **thyroid-stimulating hormone and prolactin**.

V

TREATMENT

A combination of hormonal suppression of hair growth and mechanical hair removal offers the most complete and effective treatment for patients with hirsutism.

A Goals

1. The major goal is **arresting the virilizing process**, not removing hair. Once terminal hair has been established, withdrawal of androgens does not affect the established hair pattern.
2. Amelioration of a specific disease state helps slow the rate of growth by **preventing the establishment of new hair follicles**.
3. Results may not be apparent for 6 to 12 months. Treatment of hirsutism is a **long-term process**.

B Elimination of specific causes

1. **Removal of ovarian or adrenal tumors**
2. **Suppress excess androgen production**
3. **Elimination of drugs** suspected to contribute to the abnormal hair growth
4. Treatment of Cushing's syndrome, thyroid disease, or hyperprolactinemia

C Hair removal techniques

1. **Shaving, tweezing, waxing**, and use of **depilatories** are temporary measures, which may need to be repeated daily. These methods neither stimulate hair growth nor increase the rate of hair growth.
2. **Bleaching** is effective for mild hair growth.
3. **Electrolysis** involves the permanent destruction of hair follicles. Multiple treatments are necessary, and scarring may occur. This method should be used after 6 months of hormonal therapy when new hair growth has ceased.
4. **Laser** provides directed damage to hair follicles, which temporarily or permanently removes terminal hair. This method can be used over a larger area than electrolysis, but it is not yet perfected for the treatment of hirsutism. Ideal patients are those with pale skin and very dark hair.
5. **Eflornithine HCl (Vaniqa)**. This topical medication inhibits the enzyme ornithine decarboxylase responsible for hair growth. It acts directly at the hair follicle and slows hair growth.

D Suppression of androgen synthesis

1. In most **idiopathic or ovarian-related hirsutism**, suppression of ovarian steroidogenesis is the goal.
2. **Combination hormonal contraceptives** have a potent negative feedback effect on the pituitary and other effects that ameliorate peripheral androgen stimulation. Low-dose formulations (30 to 35 μ g estrogen) are effective in treating hirsutism, and a demonstrated benefit has been shown with 20- μ g preparations. Although the progestins in the combined hormonal contraceptives are all different and have different levels of androgenicity or anti-androgenic activity, there is no proven benefit of one over another in the treatment of hirsutism. The best contraceptive is the one that is best tolerated by the individual patient.

- a. Both **estrogen** and **progestin** in the hormonal contraceptives cause a decrease in gonadotropin secretion with a consequent decrease in ovarian androgen production.
 - (1) **Estrogen** also stimulates an increase in SHBG, causing increased binding of testosterone and decreased free testosterone levels.
 - (2) **Progestin** may also displace active androgens at the hair follicle and may inhibit 5 α -reductase activity.
- b. Blood testosterone levels are effectively suppressed within 1 to 3 months of therapy. This reduction has been associated with a clinical improvement in the progression of hirsutism.
3. **Medroxyprogesterone acetate** (150 mg intramuscularly every 3 months or 10 to 20 mg orally per day) is effective in suppressing gonadotropin secretion in patients for whom oral contraceptives are contraindicated. It results in:
 - a. Decreased production of androgens caused by suppression of LH and FSH
 - b. Increased clearance of testosterone from the circulation caused by induction of liver enzymes
4. **Gonadotropin-releasing hormone (GnRH) agonists** suppress the hypothalamic–pituitary–ovarian axis, thereby decreasing ovarian steroidogenesis.
 - a. Uses
 - (1) In severely androgenized patients refractory to other therapies
 - (2) With estrogen and progesterone replacement and with calcium supplements
 - b. Side effects include hot flashes, vaginal dryness, and bone loss.
5. **Corticosteroid** suppression of adrenal androgen production is useful in more severe cases of NCAH. For mild cases of NCAH, patients can instead be managed effectively with oral contraceptives and antiandrogen therapy. Long-term side effects of corticosteroids include osteoporosis, diabetes mellitus, and avascular necrosis of the hip, which dictate careful use of this medication.

E Androgen-receptor blockers These medications inhibit binding of DHT to the androgen receptor, thus directly inhibiting hair growth. When combined with oral contraceptives, progestins, or GnRH agonists, further benefit may be obtained.

1. **Spirolactone** is an aldosterone antagonist and diuretic widely used in the United States.
 - a. This agent also inhibits 5 α -reductase and variably suppresses the ovarian and adrenal synthesis of androgens.
 - b. Side effects include initial diuresis and fatigue. Hyperkalemia and hypotension may also occur.
2. **Flutamide** is a nonsteroidal antiandrogen widely used in Europe for treatment of hirsutism.
 - a. Side effects include hepatotoxicity; liver enzymes must be monitored.
 - b. Contraception must be used with this medication because flutamide may be teratogenic to a male fetus.
3. **Cyproterone acetate** is a potent progestin and antiandrogen.
 - a. This agent inhibits gonadotropin secretion (primarily LH), which leads to decreased androgen levels.
 - b. It is not currently available in the United States, but is available in Canada and Europe. It is used as a progestin in oral contraceptives.

F Other medications

1. **Finasteride** inhibits 5 α -reductase activity with negligible side effects.
 - a. This agent blocks the conversion of testosterone to DHT.
 - b. Contraception must be used with this medication because it is considered a teratogen as it interferes with development of genitalia in a male fetus.
2. **Cimetidine** is a less potent androgen-receptor blocker, rarely used for this indication.
3. **Ketoconazole** blocks ovarian and adrenal androgen synthesis by inhibition of the cytochrome P450 system. This agent has multiple side effects, including the potential for hepatotoxicity and adrenal insufficiency. Therefore, it is rarely used for hirsutism.
4. **Insulin-sensitizing agents.** Metformin and thiazolidinediones are being used in patients with PCOS to improve insulin sensitivity, thus decreasing hyperinsulinemia and androgen levels. Improvement in menstrual cyclicity has been demonstrated, but do not appear to improve hirsutism. These agents are not approved by the U.S. Food and Drug Administration for treatment of hirsutism.



Study Questions for Chapter 25

Directions: Match the appropriate hormone(s), substance, or enzyme (which you could measure) with the description that is most likely to account for excessive hair growth in a woman. Each answer may be used once, more than once, or not at all.

QUESTIONS 1–3

- ☐ A Testosterone
- ☐ B 3 α -Androstenediol glucuronide
- ☐ C Androstenedione
- ☐ D 5 α -Reductase
- ☐ E 17-Hydroxyprogesterone

1. Rapidly progressive hirsutism
2. Hirsutism in a woman with regular menses and no abnormal hormonal measurements
3. Gradual onset around puberty of hirsutism and menstrual irregularity

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

QUESTIONS 4–6

4. A 33-year-old woman, gravida 2, para 1, spontaneous abortion 1, presents to your office reporting increasing dark hair growth on her chin, upper lip, and lower abdomen. This growth has occurred over many years and has forced her to wax and bleach more often. She denies changes in her voice or size of her clitoris, reduction in breast size, or acne. During her early teen years, she had regular menstrual periods that lasted 4 to 5 days. Her menstrual cycles have become unpredictable and she is currently on combined oral contraceptive to regulate her cycle. Her past medical history is significant for hepatitis C, which she acquired from a blood transfusion to treat postpartum hemorrhage with her first pregnancy. The next best step in the management of hirsutism in this patient is:

- ☐ A Depomedroxyprogesterone acetate
- ☐ B Flutamide
- ☐ C Spironolactone
- ☐ D Dexamethasone
- ☐ E Leuprolide

5. A 23-year-old woman, gravida 1, para 0, abortion 1, has irregular, unpredictable menstrual periods every 30 to 90 days. Physical examination reveals acne on her face and back and several dark, coarse hairs on her chin and lower abdomen. The initial step in diagnosis of androgen excess in this woman is to measure which of the following?

- ☐ A Androstenedione
- ☐ B Dehydroepiandrosterone sulfate
- ☐ C LH and FSH
- ☐ D 17-Hydroxyprogesterone
- ☐ E 5 α -Reductase

6. A 22-year-old African American female presents to your office complaining of severe hirsutism on her face. She is currently shaving daily and is very distressed. After you evaluate her you diagnose PCOS. You give her what advice for the best way to manage her hirsutism symptoms?

- ☐ A Shaving is bad because it makes the hair grow faster
- ☐ B She would be a good candidate for laser epilation
- ☐ C Medroxyprogesterone acetate is the best option
- ☐ D Combined hormonal contraception with spironolactone is the best option
- ☐ E Metformin therapy for PCOS is the best option



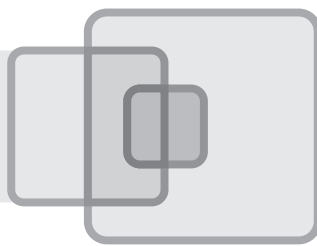
Answers and Explanations

1. **C** [III B 1 b], 2. **D** [II C 3], 3. **E** [III A 2]. Rapid progression of hair growth is suggestive of an androgen-producing tumor. Testosterone is the most likely hormone produced by an ovarian or adrenal tumor. Androstenedione is rarely associated with tumor. Excessive hair growth is caused by the concentration of hair follicles in the skin (which is genetically determined), degree of 5α -reductase activity, and the sensitivity or response of hair follicles to DHT. 3α -Androstanediol glucuronide is the peripheral tissue metabolite of DHT. It is rarely measured for clinical purposes. NCAH presents at puberty and is characterized by gradual onset of hirsutism and menstrual irregularity. The most common form is caused by deficiency in 21 -hydroxylase which leads to a build-up of 17 -OHP from the adrenal gland. Diagnosis is made by demonstrating elevated serum 17 -OHP. This condition must be distinguished from PCOS. In PCOS, testosterone is not always elevated.

4. **The answer is C** [IV E 1]. The best complement to oral contraceptive pills (OCPs) in the treatment of hirsutism is spironolactone. The mechanism is as follows: it binds to the androgen receptor, preventing the binding of DHT and thus inhibiting hair growth; it also inhibits 5α -reductase and thus the production of DHT. Depomedroxyprogesterone acetate works similarly to OCPs in that it suppresses gonadotropins, which decrease ovarian androgen production, but it does not increase SHBG, and therefore does not achieve the same effect. Flutamide, another androgen-receptor blocker, is contraindicated in this woman because of hepatotoxicity. Dexamethasone, a glucocorticoid, suppresses pituitary corticotropin and thus adrenal androgen production, but this drug is used only in patients with elevated adrenal androgen production. GnRH agonists suppress the hypothalamic–pituitary–ovarian axis, which decreases ovarian stimulation and steroidogenesis. This medication is used infrequently for this indication and is not added to OCPs.

5. **The answer is D** [II A 1]. This patient most likely has PCOS because she has menstrual irregularity and clinical evidence of hyperandrogenism. Therefore, to confirm this diagnosis, all other causes of these symptoms must be excluded. For this reason, a 17 -OHP level must be drawn at 8 AM and just following a menstrual period to evaluate for NCAH. Measuring androstenedione is not going to make a diagnosis. DHEAS is likely to be mildly elevated in several hyperandrogenic syndromes, but the time course of this patient's symptoms does not suggest a tumor, so DHEAS should not be measured. One cannot measure 5α -reductase. 5α -Reductase activity reflects levels of DHT at the skin and can be evaluated by measuring levels of the 3α -androstanediol glucuronide. The LH-to-FSH ratio may be elevated in PCOS, but it is not diagnostic of PCOS and therefore is not necessary.

6. **The answer is D** [IV A, D, E]. The best treatment option for this young woman is combined hormonal contraceptive with spironolactone. The best results with treating hirsutism are achieved by using more than one modality to stop hair growth, and by using these two medications, androgens are decreased; free androgens are decreased by increasing SHBG and the action of androgens. It would also be good to maximize hair removal procedures to get rid of the hair she already has. Electrolysis would be preferable to laser: since she has dark pigmented skin, laser would not be effective. Shaving can be continued since it does not increase the rate of hair growth. Metformin has not been proven to treat hirsutism in women with PCOS. Medroxyprogesterone acetate would not be as effective as the combined hormonal contraceptive.



Pelvic Pain

ISAAC E. SASSON • SAMANTHA M. PFEIFER

I

INTRODUCTION

Chronic pelvic pain syndrome is estimated to account for 10% of all visits to gynecologists. Afflicted women report continuous lower abdominal and pelvic pain that markedly hinders their daily activities. Although **acute pelvic pain may be associated with life-threatening illness**, chronic pelvic pain may also have a devastating impact on patients, and physicians should remain compassionate and empathetic. Pain is a subjective experience. The lack of physical findings does not in any way negate the significance of a patient's pain. The **psychological effects** may be considerable.

- A** The risk of major **depression, sexual dysfunction, and substance abuse** is increased.
- B** The prevalence of **childhood or adult sexual abuse** is particularly high, and the rate of marital and sexual dysfunction is greater among this cohort of patients.
- C** Psychological counseling and testing may be necessary to identify patients who require more extensive therapy.

II

DEFINITION

Pelvic pain can be acute or chronic, and can be caused by a multitude of conditions in many organ systems. Just because the pain is pelvic in location does not mean that the cause of the condition is gynecologic.

- A** **Acute pelvic pain** (Table 26–1) is pain that is located in the anatomic pelvis and is of short duration and sudden onset.
- B** **Chronic pelvic pain** (Table 26–2) is noncyclic pain of 6 or more months' duration that localizes to the anatomic pelvis, the anterior abdominal wall at or below the umbilicus, the lumbosacral back, or the buttocks and is of sufficient severity to cause functional disability or lead to medical care.
 1. 15% to 20% of women ages 18 to 50 have pelvic pain for more than 1 year
 2. **25% to 50% of patients with chronic pelvic pain have more than one etiology**
 3. Intensity and consistency of pain is greater in women with multiorgan system symptoms

III

ANATOMY AND PHYSIOLOGY OF PELVIC PAIN

Pain perception involves an integration of multiple stimuli through a network of neuronal pathways. Visceral pain is more diffuse than somatic pain, probably because there is no specific identification within the cerebral sensory cortex.

- A** **Neuroanatomy** The pelvic organs receive their innervation from the **autonomic nervous system**, which is composed of both sympathetic and parasympathetic fibers.
 1. **Sympathetic nerves** are used to transmit most afferent stimuli through cell bodies that lie in the **thoracolumbar** distribution. Areas that are müllerian in embryonic origin (e.g., uterus, fallopian tubes, and upper vagina) transmit impulses via sympathetic fibers into the spinal cord at the level of T10, T11, T12, and L1. Impulses from the uterus travel through the uterosacral ligaments to the uterine inferior plexus. From the uterus, they join other pelvic afferents to form the hypogastric

TABLE 26–1 Causes of Acute Pelvic Pain

Gynecologic	Gastrointestinal	Urologic
Ovarian cyst	Appendicitis	Cystitis
Acute pelvic inflammatory disease	Diverticulosis	Urolithiasis
Adnexal torsion		Pyelonephritis
Ectopic pregnancy		
Endometriosis		
Ruptured ovarian cyst		
Leiomyoma		
Endometritis		

plexus at the level of the rectum and vagina. The ovaries and distal fallopian tubes derive their nerve supply independently and enter the spinal cord at T9 and T10.

2. **Parasympathetic nerve fibers** are also involved to a lesser extent in the transition of painful stimuli. Impulses from the upper vagina, cervix, and lower uterine segment travel through the parasympathetic system to the sacral roots S2 to S4.
3. **Both sympathetic and parasympathetic fibers** innervate the bladder, rectum, perineum, and anus, which are derived from the urogenital sinus. Fibers from the perineum and anus combine to form branches of the pudendal nerve, eventually terminating in the second and fourth sacral root.

B Physiology Pelvic pain is visceral and may be either **referred** or **splanchnic**.

1. **Splanchnic pain** occurs when an irritable stimulus is appreciated in a specific organ secondary to tension (stretching, distention, or pulling), peritoneal irritation or inflammation, hypoxia or necrosis of viscera, or production of prostanoids.
2. **Referred pain** occurs when autonomic impulses arise from a diseased visceral organ, eliciting an irritable response within the spinal cord. Pain is sensed in the dermatomes corresponding to cells receiving those impulses.

IV

DIFFERENTIAL DIAGNOSIS

A Acute pelvic pain (Table 26–1)

1. **Ectopic pregnancy** (see Chapter 30). It is paramount to exclude the possibility of an **ectopic tubal gestation**, a life-threatening condition.

TABLE 26–2 Causes of Chronic Pelvic Pain

Gynecologic	Gastrointestinal	Urologic	Musculoskeletal	Psychological
Endometriosis	Constipation	Urinary tract infection	Postural	Depression
Pelvic inflammatory disease/tubo-ovarian abscess	Irritable bowel	Kidney stones	Trigger points	Sexual abuse
Adhesive disease	Gastroenteritis	Interstitial cystitis	Joint pain	Substance abuse
Congenital anomalies	Lactose intolerance	Urethral syndrome	Inflammation	Eating disorder
Ovarian masses	Inflammatory bowel disease		Spinal injury	
Chronic ectopic pregnancy	Appendicitis			
Dysmenorrhea	Hernia			
Leiomyoma				
Endometritis				

- a. **Pelvic pain** occurs as a result of distention of the fallopian tube caused by the growing pregnancy. The pain is usually **unilateral**. If the pregnancy ruptures through the fallopian tube, rebound tenderness may occur.
 - b. **Shoulder pain** may develop as a result of blood in the abdomen causing diaphragmatic irritation and stimulating the phrenic nerves.
 - c. A **pregnancy test is mandated in any woman of childbearing age who presents with acute pelvic pain**. If the test is positive, the presence of an ectopic pregnancy must be excluded from the differential diagnosis, particularly in patients with abnormal uterine bleeding.
2. **Ruptured ovarian cyst**. Midcycle pain or **mittelschmerz** is pain in the lower abdomen noticed at or near the time of ovulation. It is believed to be secondary to chemical irritation of the peritoneum from ovarian follicular cyst fluid after ovulation. The pain usually lasts only a few hours and usually no more than 2 days. The use of ultrasonic visualization of the ovaries most often confirms or excludes this diagnosis.
 3. **Ovarian torsion**. This involves twisting of the ovary and/or tube and occluding the blood supply. Acute lower abdominal pain may be the primary manifestation.
 - a. The clinical presentation is usually a history of sudden onset of pain accompanied by nausea and vomiting. The severity depends on the extent of interference with the ovarian blood supply. Intermittent torsion can present as intermittent pelvic pain. The more extensive the ischemia, the more severe the pelvic pain. The pain is usually paroxysmal and unilateral but becomes more constant if infarction occurs. It is associated with peritoneal signs and an elevated white blood cell (WBC) count.
 - b. Documentation of ovarian blood flow by **color Doppler ultrasound** is a helpful diagnostic modality in evaluating this medical emergency, but it is not always accurate. Diagnosis is made on clinical presentation, and **laparoscopy** must be performed to confirm the diagnosis.
 4. **Pelvic inflammatory disease (PID)**. Pelvic pain that is acute in onset and associated with cervical motion tenderness and febrile morbidity is characteristic of PID (see Chapter 34). Rebound tenderness and a partial ileus may result from the presence of purulent material within the pelvic and abdominal cavity. In women diagnosed with acute PID, 18% to 35% will develop chronic pelvic pain.

B Chronic or recurrent pelvic pain (Table 26–2)

1. **Dysmenorrhea** is painful menstruation. It is considered **primary** if it occurs in the absence of identifiable pathology. **Secondary dysmenorrhea** is caused by a defined pelvic abnormality, such as endometriosis or müllerian anomaly.
 - a. The pain is usually spasmodic or throbbing. It is usually located diffusely in the lower abdomen and may radiate to the lower back and legs.
 - b. Its onset is concurrent with menses, and the pain lasts for 1 to 3 days.
 - c. The etiology of painful uterine contractions involves **prostaglandin F_{2α}** produced in the endometrial cells by the action of phospholipase A₂ on lipid cell membranes, forming arachidonic acid.
 - d. Associated symptoms include backache, nausea, vomiting, diarrhea, headache, and fatigue.
2. **Endometriosis** is characterized by the presence of endometrial glands and stroma outside the uterine cavity (see Chapter 27). The mechanism of pain from endometriosis is hypothesized to be cyclic focal bleeding from peritoneal implants, the inflammatory cytokines released from an increased number of peritoneal immune cells, and from irritation or infiltration of the pelvic floor nerves.
 - a. **Etiology**. The mechanism of development of endometriosis is still being investigated. Theories include retrograde menstruation, metastases via vascular and lymphatic channels, altered immune response to ectopic endometrial tissue, and metaplastic transformation of totipotent cells.
 - b. **Pain symptoms**
 - (1) The burden of disease does not correlate with the degree of pain.
 - (2) Lesions are hormonally responsive resulting in pain that worsens pre- and during menstruation.
 - (3) Deep dyspareunia that is positional suggests a diagnosis of endometriosis as nodular endometriotic lesions in the pelvis may be irritated by intercourse.

c. Diagnosis

- (1) The definitive diagnostic test is laparoscopy. Approximately 25% to 40% of patients who undergo laparoscopy for chronic pelvic pain have evidence of endometriosis. Visualization of lesions is sufficient for diagnosis. Biopsy of lesions is not essential.
 - (2) At laparoscopy lesions can be red vesicular, vascular lesions; black “powder burn” lesions; or white largely fibrous lesions.
3. **Adenomyosis**, a condition characterized by the presence of ectopic foci of endometrium within the myometrium, may also cause chronic pelvic pain and severe dysmenorrhea and is also associated with menorrhagia. Magnetic resonance imaging (MRI) is a useful modality to diagnose adenomyosis and to better plan treatment. Definitive diagnosis is by pathological examination.
 4. **Chronic PID and tubo-ovarian abscess (TOA)**
 - a. Chronic salpingo-oophoritis can lead to pelvic pain. Hydrosalpinges can become reinfected causing significant pain, fever, and occasionally sepsis and death. Initial infection that damages the fallopian tubes may be asymptomatic, for example Chlamydia, so an acute presentation may not precede the chronic sequelae.
 - b. The organisms in TOA are primarily gut flora, not gonorrhea or Chlamydia.
 - c. Antibiotic therapy is the first-line treatment. Radiologic drainage of abscesses can be used if there is slow response to antibiotics. However, conservative management of TOA is associated with a 24% risk of developing chronic pain.
 - d. Surgery is reserved for those who do not respond to medical therapy. Due to extensive infection and inflammation, surgical therapy will often necessitate removal of both ovaries, fallopian tubes, and even the uterus and therefore should be considered carefully in a young reproductive age woman.
 5. **Adnexal masses.** Cysts or tumors on the ovaries or paratubal cysts can cause pain. Diagnosis is best made by ultrasound. Functional cysts can be managed expectantly as they should resolve; however, tumors are treated surgically.
 6. **Müllerian anomalies** may result in an obstructed outflow tract associated with pelvic pain (see Chapter 21).
 - a. A complete obstruction is associated with amenorrhea. This can lead to chronic pelvic pain if there is functional endometrium in an obstructed uterine remnant, or if an obstruction in the outflow tract has led to significant endometriosis and adhesive disease due to retrograde menstrual flow in the setting of delayed diagnosis.
 - b. A partial obstruction of part of the müllerian structures that allows regular menstruation. This category would include conditions such as a noncommunicating obstructed uterine horn, an obstructed hemi-vagina associated with a duplicated cervix and uterine didelphys, and septate or bicornuate uterine fundus.
 - c. It is important to consider the diagnosis of obstructed müllerian anomaly when there is increasing dysmenorrhea in a young female that is not responding to medical therapy, and also in the case of müllerian agenesis when pelvic pain is present. Early diagnosis is important.
 - d. Müllerian anomaly should always be considered when there is a history of renal anomalies, such as renal agenesis, as the conditions are associated. With the common use of prenatal ultrasound, many individuals will know if they have a renal anomaly.
 - e. MRI is the best way to diagnose müllerian anomalies. These are rare and many radiologists are not familiar with the many configurations that can exist. Careful review of the films is important.
 - f. Surgical correction is the treatment of choice.
 7. **Leiomyomata** (see Chapter 28) may also cause pelvic pain. Mechanisms include: fibroid degeneration causing pain, dysmenorrhea due to passage of large blood clots associated with menorrhagia, and cramping associated with passage of large intracavitary fibroid through the cervix. Pressure symptoms, constipation and urinary frequency can occur depending on the size and location of the fibroids.

C Urologic disorders

1. **Interstitial cystitis (IC)** is a poorly understood, chronic inflammatory condition of the bladder wall. It has an estimated prevalence of 5 cases per 1,000, with women affected 10 times more than men. Seventy percent of women with IC present with chronic pelvic pain.

- a. Symptoms include pelvic pain with filling of the bladder that is relieved with voiding. This manifests as urinary frequency, urgency, and pain.
 - b. Other frequently observed symptoms include dyspareunia, premenstrual flare of symptoms, and generalized pelvic pain. These symptoms can be confused with those of endometriosis.
 - c. In women with IC a voiding diary often demonstrates 20 or more voids in a 24-hour period with three episodes of nocturia and average voided volumes of 100 mL (low).
2. Other urologic conditions that may lead to lower abdominal pelvic pain include urethral syndromes, bladder malignancy, acute or chronic urinary tract infections, and renal lithiasis.

D Gastrointestinal disorders

1. Acute conditions

- a. **Appendicitis:** The pain is initially not well localized because it results from luminal distention of the appendix by inflammatory exudates. However, the pain eventually localizes to the right lower quadrant when the parietal peritoneum becomes locally involved in the inflammatory process.
- b. **Diverticulitis:** Most commonly observed in older women. Usually left-sided pain.

2. Chronic conditions

- a. **Irritable bowel syndrome (IBS)** is a functional bowel syndrome of undetermined etiology. Patients present with relapsing and remitting abdominopelvic pain associated with bloating and bowel dysfunction (diarrhea, constipation, or both).
 - (1) IBS affects 15% of adults, and twice as many women than men. IBS symptoms are found in 50% to 80% of women with chronic pelvic pain.
 - (2) Diagnosis of IBS is likely in patients with two of three features: pain relieved by defecation, pain associated with a change in frequency of stool, or pain associated with a change in stool form. Associated features include abnormal stool frequency (more than 3/d or fewer than 3/wk), or 25% of bowel movements affected by abnormal stool form, abnormal stool passage, passage of mucus, or feelings of bloating or distension.
- b. Other gastrointestinal causes of chronic pelvic pain include constipation, inflammatory bowel disease, and carcinoma of the colon.

E Musculoskeletal disorders Pain is most commonly due to repetitive stress and strain associated with the typical pelvic pain posture, increased lumbar lordosis and anterior tilt of the pelvis. This posture enables weak and deconditioned muscles to form an imbalance in the pelvis resulting in formation of trigger point, hypertonicity, and increased pelvic pain.

- 1. **Abdominal trigger points** are defined as a focus of hyperirritability in a muscle or its fascia that is symptomatic with respect to pain. These areas are always tender and prevent full lengthening of the muscle. Typically the pain improves with rest and is exacerbated with activity.
- 2. Other musculoskeletal causes include **myofascial pain syndromes**, **fibromyalgia**, compression of lower vertebrae, and chronic back pain.

F Pelvic adhesive disease The relationship between pelvic adhesive disease and chronic pelvic pain remains complicated and controversial. The incidence of pelvic adhesions in patients with pelvic pain is similar to those without chronic pain. Furthermore, the extent of adhesive disease does not correlate with the severity of the patient's symptoms.

- 1. **Etiology.** Adhesion formation occurs after trauma to the visceral or parietal peritoneum. Peritoneal injury results from the inflammatory cascade that is precipitated by **infection**, **endometriosis**, and **operative procedures** (70% of cases). Tissue injury during surgery results from mechanical abrasion, thermal trauma, desiccation, and foreign material (talc, gauze, and suture material). Other causes include radiation and ischemic injury.
- 2. **Pathogenesis**
 - a. Triggers precipitate a molecular cascade that results in fibrin deposition at the site of injury, which can bridge adjoining tissues. Adhesion formation is determined within 72 hours of injury. If adequate fibrinolysis occurs, the peritoneal membrane is re-epithelialized and adhesions do not form. However, trauma induced suppression of the fibrinolytic cascade results in persistence of the fibrin bridges, invasion of fibroblasts into the affected area, neovascularization, and subsequently, adhesion formation.

b. **Mechanical components** have been proposed as the underlying mechanism of pain sensation caused by adhesions. Patients experience pain via mechanical stimulation of visceral nociceptors because of mechanical stretching of internal organs.

3. Diagnosis

- a. Patients with adhesions may often have a history of previous pelvic surgery, but many have no past history that may supply a reason for the existence of adhesions. Physical examination of the patient may also be noncontributory. Approximately 25% of patients with adhesions have no preoperative findings on physical examination, which suggests the presence of adhesions.
- b. **Laparoscopic visualization of the abdomen and pelvis is essential.** Detectable pathologic findings are documented in approximately 60% of patients; in 25% of these patients, adhesions are the primary condition.

G Physical and sexual abuse

1. There is a significant association between a history of abuse and chronic pain syndromes. A total of 40% to 50% of patients with chronic pelvic pain report a history of abuse. In all women with chronic pelvic pain should be screened for a history of abuse, and it is important to ensure they are not currently being abused or in danger.
2. The mechanism by which abuse results in chronic pelvic pain is poorly understood. Abuse may result in a lower pain threshold in survivors and that chronic stimulation may heighten sensitivity resulting in persistent abdominal, pelvic, or bowel pain.

V

EVALUATION

A **Important factors** to assess when determining the clinical significance of pelvic pain include:

1. **Onset** of the pain
2. **Relationship to the menstrual cycle** (Is the pain constant or does it vary?)
3. **Character** of the pain
4. **Location** of the pain
5. **Severity** of the pain (Does it interfere with activities of daily life?)
6. **Presence of associated symptoms:** premenstrual spotting, dyschezia, dysmenorrhea, and deep dyspareunia are suggestive of endometriosis. Any other symptoms, such as fever, chills, nausea, vomiting, or anorexia, should also be noted
7. **Impact on quality of life:** progressively worsening symptoms, missing work or school, and avoiding social interactions
8. **Identification of risk factors:** previous abdominopelvic surgery, history of an abusive relationship
9. **Physical examination:** uterine size, texture and mobility, presence of fibroids or adenexal masses, nodularity along the uterosacral ligaments

B **Imaging** studies are useful in determining the etiology of pelvic pain.

1. **Pelvic ultrasound** is particularly useful in identifying abnormalities of gynecologic structures.
2. **Pelvic MRI** may provide additional details when abnormalities are identified. It is particularly important in diagnosing müllerian anomalies, detecting size and location of fibroids, diagnosing adenomyosis, and further evaluating adnexal pathology.

C **Laparoscopy**, the endoscopic assessment of abdominal and pelvic pathology, is the **gold standard** for the diagnosis of pelvic pain.

1. Laparoscopy is indicated in cases of pelvic pain that are unresponsive to medical therapy or when an organic cause of the pain is suspected.
2. Approximately 40% of laparoscopies are reportedly performed in cases of chronic pelvic pain.
3. Endometriosis and adhesions account for 90% of the diagnosis when abnormalities are identified laparoscopically.

4. Adolescents should also be considered candidates for diagnostic laparoscopy despite their age since endometriosis is seen in 60% to 70% of adolescents undergoing laparoscopy for chronic pelvic pain.
5. Laparoscopy is diagnostic. However, disease identified at laparoscopy can and should be surgically treated during the procedure.

D Evaluation of the urinary tract

1. Initial evaluation should include a urinalysis, urine culture, and cytology that demonstrate signs of inflammation without infection or malignancy.
2. The Interstitial Cystitis Symptom Index is a validated questionnaire that predicts the diagnosis of IC and can be used to determine which patients would benefit from further investigation. Diagnostic criteria include urinary frequency, urgency, and pain.
3. Urodynamic evaluation demonstrates low bladder capacity.
4. Cystoscopy may reveal the characteristic lesions, glomerulations and Hunner ulcers, with bladder distension.

VI

TREATMENT

The most effective treatment for chronic pelvic pain utilizes a **multidisciplinary approach** that incorporates medical, surgical, psychological, dietary, and social interventions.

A Acute gynecological conditions

1. **Ectopic pregnancy** can be managed medically or surgically. Medical management of ectopic pregnancy is described in Chapter 30. Patients with an ectopic pregnancy who present with acute abdominal pain are managed surgically.
2. **Ruptured ovarian cyst** can be managed with conservative therapy, oral pain medication, and observation.
3. **Ovarian torsion** is confirmed laparoscopy. If the ovary appears viable, it may be untwisted and a cystectomy performed. If necrotic, the ovary and tube must usually be removed. Hence, early diagnosis helps preserve ovaries.
4. **PID** is managed medically, often with oral antibiotics. Criteria for hospitalization and parenteral antibiotic therapy are described in Chapter 34.

B Chronic gynecological conditions: dysmenorrhea, endometriosis, adenomyosis

1. Medical management

- a. Therapy is aimed at reducing prostaglandin production. Agents such as **prostaglandin synthetase inhibitors** (nonsteroidal anti-inflammatory drugs [NSAIDs]) are useful first-line therapies. Ideally, NSAIDs should be taken continuously for the duration of the expected menstrual pain. Although NSAIDs are all similar, it is important to counsel patients that if one particular NSAID is not effective, then it is worth trying another as it may provide a better therapeutic result.
- b. **Opioids** are helpful in improving pain symptoms but fail to show an improvement in functional or psychological status. Furthermore, chronic opioid use may result in addiction.
- c. Endometriosis-associated chronic pelvic pain can be treated with combination **oral contraceptive pills** (OCPs) or combined transdermal preparations. There is some evidence that using these medications in a continuous fashion to prevent menstruation and promote amenorrhea may be more effective in controlling pain symptoms. Progestins alone are also effective in treating endometriosis-associated pain and can be administered as an oral regimen, in a depot preparation, or a progestin secreting IUD. Hormonal therapy is effective in suppressing ovulation and menstruation, stabilizing estrogen and progesterone levels, decreasing menstrual fluctuations in prostaglandin levels and ultimately reducing chronic pain symptoms.
- d. **GnRH agonists** can be used to suppress menses and create a hypoestrogenic environment. Concerns with these medications include hypoestrogenic side effects and permanent decrease in bone density with use greater than 6 months. Long-term treatment can be given with an

add-back therapy to decrease side effects and bone loss utilizing norethindrone acetate alone, or in combination with a low-dose estrogen preparation.

- e. **Aromatase inhibitors** are currently being investigated for use with GnRH agonists or combined hormonal contraceptives for the management of pain associated with endometriosis.

2. Surgical management

- a. **Laparoscopy** is indicated in a woman who has dysmenorrhea or chronic pelvic pain that is unresponsive to NSAIDs and combined hormonal contraception or progestin-only contraception. The advantage is primarily diagnostic, however, surgical treatment of causes of pain can be performed at that time. Excision or destruction of endometriotic lesions during laparoscopy results in pain relief for 45% to 85% of women.
- b. **Hysterectomy** with or without bilateral salpingoophorectomy results in relief from chronic pelvic pain in 75% of women.
- c. **Presacral neurectomy** can be used to treat central dysmenorrhea, with little effect on nonmenstrual pain or dysmenorrhea. This procedure is technically difficult and should only be performed by an experienced surgeon.
- d. **Laparoscopic uterine nerve ablation (LUNA)** is performed by transecting the uterosacral ligaments at their insertion to the uterus thereby interrupting the cervical sensory fibers. However, LUNA is no longer recommended as there is no evidence it improves pelvic pain from endometriosis or nonmenstrual etiologies.

3. Urologic disorders are targeted to specific diseases and are often managed by a urologist or a urogynecologist.

- a. **Interstitial cystitis.** Primary treatment includes diet modification with avoidance of acid-rich foods including caffeine, tomatoes, alcohol, and chocolate, systemic therapy with pentosan polysulfate sodium (Elmiron), and bladder instillation therapy with dimethyl sulfoxide (DMSO).

4. Gastrointestinal disorders are targeted to specific diseases and are often managed by an internal medicine physician or a gastroenterologist.

5. Musculoskeletal disorders

- a. Physical therapy is the mainstay of therapy for musculoskeletal disorders. Myofascial trigger points of the pelvic floor show improvement of pain in 65% to 70% of patients treated with pelvic floor muscle relaxation therapy.
- b. Injections with long acting local anesthetic can be used to treat myofascial points of the abdominal wall, vagina, and sacrum. A response rate of 68% has been demonstrated in the setting of chronic pelvic pain.

6. Pelvic adhesive disease

- a. Laparoscopic lysis of adhesions in patients with chronic pelvic pain results in improvement of symptomatology in 65% to 85% of cases in the setting of patients with dense adhesions involving the bowel. This improvement is maintained in approximately 75% of patients 6 to 12 months after surgery.
- b. However, laparoscopic lysis of adhesions is not more effective than diagnostic laparoscopy without adhesiolysis. Considering that the rate of adhesion reformation after laparoscopic adhesiolysis is estimated to be as high as 85%, and the risk of intestinal perforation during the procedure ranges from 10% to 25%, the role of this procedure in the management of chronic pelvic pain remains suspect.



Study Questions for Chapter 26

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A 14-year-old adolescent, gravida 0, presents to your office with 1 year of debilitating, cramping with her menses, predominantly on the left side. She was taking NSAIDs which initially did help, but now her pain is no longer well controlled. Her past medical history is significant for IBS, congenital left renal agenesis, and a ruptured appendix at 8 years of age. She denies any sexual activity. The next step would be:

- ☐ A Try another NSAID
- ☐ B Oral contraceptive pills
- ☐ C Laparoscopy
- ☐ D Vaginal ultrasound
- ☐ E MRI

2. A 28-year-old female, gravida 0, presents to your office for 18 months of progressively worsening pelvic pain. Her pain is 8/10 in severity, deep in the midline in lower abdomen. She reports that her pain begins 3 days before her period and worsens with the onset of menses. She has started to miss work on the first day of her menses. She treats her symptoms with NSAIDs with some relief, and has tried several different ones. She reports deep dyspareunia. Her pelvic examination is normal. The next best step is:

- ☐ A Vaginal ultrasound
- ☐ B Laparoscopy
- ☐ C Continuous combined oral contraceptive
- ☐ D Aromatase inhibitors
- ☐ E GnRH agonist with add back

3. A 28-year-old woman, gravida 0, presents for evaluation of worsening chronic pelvic pain. She had been diagnosis with endometriosis by diagnostic laparoscopy 6 years prior but had been lost to care since that time. She reports cyclic, left-sided pelvic pain that is no longer controlled with NSAIDs. On physical examination, she is noted to have thickening and nodularity of her left uterosacral ligament and her cervix is deviated to the right. She has no uterine, cervical, or right adnexal tenderness. She is noted to have 5 cm left adnexal mass, which is tender to palpation and fixed to the pelvic sidewall. Transvaginal ultrasound demonstrates a 4.5-cm complex left ovarian cyst consistent with an endometrioma. The next best step in management of this patient is:

- ☐ A Medical treatment with a continuous OCPs
- ☐ B Medical treatment with a GnRH agonist
- ☐ C Laparoscopy with ablation of endometriosis and a left ovarian cystectomy
- ☐ D Referral for urodynamic evaluation and cystoscopy
- ☐ E Hysterectomy and left salpingoophorectomy

4. A 36-year-old woman, gravida 0, with a history of endometriosis noted at a laparoscopy performed for pelvic pain 5 years ago presents for a second opinion for evaluation of worsening pelvic pain. Her endometriosis has been poorly controlled with combined oral contraceptives. Over the past 8 months she has noted worsening dysmenorrhea, dyspareunia with deep penetration, and increased constipation. She also states that her endometriosis is making her urinate two to three times a night. She has been taking NSAIDs maximum dose daily with little relief. She has taken GnRH agonists in the past year for treatment for endometriosis without relief of her symptoms. Your next step would be:

- ☐ A Hysterectomy
- ☐ B GnRH agonist therapy with add back
- ☐ C Aromatase inhibitors
- ☐ D Urologic evaluation
- ☐ E Depo medroxyprogesterone acetate

5. A 40-year-old woman, gravida 3, para 3, presents for severe central dysmenorrhea, 8/10 in severity associated with menorrhagia. Her pain is nonradiating, she has no exacerbating or mitigating factors. She finds little relief with NSAIDs. Her pain has been getting progressively worse since the cesarean delivery of her last child, 2 years prior. That delivery was complicated by chorioamionitis, endometritis, and subsequent wound infection. Transvaginal ultrasound demonstrated an 11-cm enlarged uterus without obvious pathologic findings. MRI of the pelvis is significant for adenomyosis. The patient reports that she has completed her childbearing. All of the following her appropriate plans of care except:

- ☐ A Laparoscopic lysis of adhesions
- ☐ B Hysterectomy
- ☐ C GnRH agonist therapy
- ☐ D Progestin secreting IUD
- ☐ E Continuous OCPs

6. A 32-year-old woman, gravida 1, para 1, with last menstrual period 10 days ago presents with a sudden onset of right lower quadrant pain that started at 7:45 AM yesterday morning after her exercise class at the gym. She developed nausea and vomiting with the onset of the pain and these symptoms have continued. She denies fever, lightheadedness, dizziness, diarrhea, urinary frequency. She has regular menstrual cycles every 28 to 30 days. She has been taking NSAIDs without relief. The most likely diagnosis is:

- ☐ A Mittelschmerz
- ☐ B Appendicitis
- ☐ C Ectopic pregnancy
- ☐ D Ovarian torsion
- ☐ E Pelvic inflammatory disease

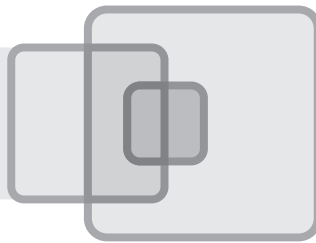


Answers and Explanations

1. **The answer is E** [IV B 6]. The patient's history of progressively worsening pelvic pain for 1 year indicates a chronic pain condition. Her history is suspicious for a partially obstructing müllerian anomaly: she had focal left lower quadrant (LLQ) pain, not diffuse, she has a history of congenital absence of the left kidney, same side as her pain, the pain is getting progressively worse over the past year. It would be important to diagnose an obstructing müllerian anomaly as soon as possible, so imaging is indicated. A transvaginal ultrasound may be traumatic for a nonsexually active 14-year-old so an abdominal ultrasound is a good place to start. Since that is not an option for answer, then next step would be to get an MRI to evaluate for müllerian anomaly. Trying another NSAID is helpful, but since her initial NSAID did work, and her symptoms are progressive and a müllerian anomaly is suspected, it is better to have a definitive diagnosis. Oral contraceptives are helpful with dysmenorrhea, but again this patient is at risk for a müllerian anomaly and this had to be excluded first. Laparoscopy is indicated once a diagnosis has been determined. Imaging prior to laparoscopy allows better planning of a therapeutic approach.
2. **The answer is C** [IV A 2 b]. The patient described had a classic presentation of endometriosis. Her pain is chronic and cyclic regularly occurs premenstrually and exacerbated by the onset of menses. She reports deep dyspareunia. She has already tried a couple of different NSAIDs. The next step would be best to start combined oral contraceptive pills, which can be taken either in a normal, cyclic fashion or continuously to improve her pain. An ultrasound can be obtained, but because her pelvic examination is normal, it would be better to treat with contraceptives for pain relief. If her symptoms do not improve with combined contraceptive pills, then ultrasound is indicated. A laparoscopy would be indicated if her pain symptoms did not respond to medical therapy with combined oral contraceptives and NSAIDs. GnRH agonists and aromatase inhibitors are advanced medical options for endometriosis and without confirmation of disease by laparoscopy, these medications are not indicated.
3. **The answer is C** [VI B 2]. The patient described has progression of her endometriosis and with a new endometrioma and involvement of her left uterosacral ligament with the nodularity noted on physical examination. The next best step in management of this patient is laparoscopy with ablation or resection of endometriosis and left ovarian cystectomy. She is young and has not been pregnant, so preserving her reproductive potential is important. Treating her surgically will improve her pain symptoms more effectively than medical therapy, and will also improve her ability to conceive. Medical treatment with OCPs may prevent progression of endometriosis in the setting of mild disease, but would unlikely to be helpful with this patient as OCP will not reduce the size of her cyst or significantly improve the pain attributed to her cyst. Medical treatment with a GnRH agonist can be considered prior to surgery for management of her suspected peritoneal disease but would do little to treat her ovarian cyst. In addition, the risks of decreased bone density with treatment of GnRH agonists must be considered. Urodynamic evaluation is not indicated in this patient. Hysterectomy in a nulligravid 28-year-old is the last option and should be only considered if symptoms are proven to be only from endometriosis, are debilitating and unresponsive to other less aggressive treatment options.
4. **The answer is D** [II B 2]. The patient described has symptoms consistent with endometriosis, however, these symptoms are progressing on therapy for endometriosis. She also has worsening dyspareunia, nocturia, and constipation and her symptoms did not respond to GnRH agonists. At this point another diagnosis in addition to endometriosis should be considered. It must be remembered that 25% to 50% of patients with chronic pelvic pain have more than one etiology and a multidisciplinary approach in managing these patients is best. The next best step would be referral to a urologist for evaluation of IC given her symptoms of urinary frequency, that she is assuming is due to endometriosis but may not be, and her dyspareunia. A gastrointestinal evaluation would also be indicated due to her constipation. GnRH agonist with add back, aromatase inhibitors, and depo-medroxyprogesterone acetate are all therapies for endometriosis and should not be considered until other causes of her pain have been excluded. A hysterectomy would also not be indicated as her pain may not be due just to endometriosis and therefore would potentially not help her symptoms and would take away her ability to have a child.

5. **The answer is A** [VI B]. The patient described has adenomyosis, which accounts for her central dysmenorrhea. Her obstetrical history which had been complicated by infection suggests the possibility of pelvic adhesive disease which may cause chronic pelvic pain but unlikely to cause dysmenorrhea or menorrhagia. Therapy should be directed to treating her primary pathology. As such, a laparoscopic lysis of adhesions would not be indicated as the primary treatment plan for this patient. Adenomyosis can be treated medically or surgically. Medical therapy includes a GnRH agonist, continuous OCPs, or a progestin secreting IUD. Surgical management with a hysterectomy would also be indicated and may be the best option in this woman who has completed her childbearing. Her ovaries would not have to be removed so she would still have her endogenous production of hormones.

6. **The answer is D** [IV 3 a]. The patient has sudden onset of pain associated with nausea and vomiting that has persisted for 1 day. The most likely diagnosis is ovarian torsion. It is important to make this diagnosis in a timely fashion as delaying will result in loss of an ovary. Mittelschmerz is less likely as this patient is cycle Day 10 and ovulation should not happen until cycle Day 14 given she has 28 to 30 day cycles. In addition, the pain associated with ruptured cyst or mittelschmerz usually lasts only a few hours, rarely longer. Appendicitis is possible, but appendicitis usually presents with nausea and vomiting with pain subsequently localizing to the right lower quadrant. Ectopic pregnancy is also possible, however the patient has not had any abnormal bleeding and she is only cycle Day 10. A pregnancy test should be done to exclude this as a possible diagnosis. PID usually presents with pain and fever that is lower pelvic and diffuse.



Endometriosis

WINIFRED MAK • SCOTT E. EDWARDS

I

INTRODUCTION

A Definitions

1. Endometriosis is the **presence of functioning endometrial glands and stroma outside their usual location** within the uterine cavity. Significant pelvic adhesions with or without associated inflammatory cells or hemosiderin-laden macrophages often result.
2. Endometriosis is **primarily a pelvic disease** with implants in, or adhesions of, the ovaries, fallopian tubes, uterosacral ligaments, rectosigmoid, bladder, and appendix. Less commonly, endometriosis can be found outside the pelvis, suggesting a metastatic spread.
3. This **generally benign disease** usually affects women in their reproductive years. However, there have been several case reports of endometrioid carcinoma developing within foci of endometriosis.

- B Incidence** The estimated incidence of endometriosis is 10% to 15%. Data suggest that 30% to 40% of patients with infertility may have endometriosis. In addition, studies suggest a hereditary tendency of this disease; individuals in certain families tend to develop the more severe and recurrent forms of endometriosis.

II

ETIOLOGY

A Causes

1. **Retrograde menstrual flow.** This theory, initially postulated by Dr. John Sampson in the early 20th century, postulates that the retrograde flow of menstrual debris through the fallopian tubes causes the endometrial cells to spread into the pelvis, form implants there, or serve as irritative foci, which stimulate coelomic metaplasia and differentiation of the peritoneal cells into endometrial-type tissue.
 - a. **Clinical evidence.** Endometriosis is commonly found in dependent portions of the pelvis, most frequently on the ovaries, cul-de-sac, and uterosacral ligaments. Menstrual efflux from fallopian tubes has been observed during laparoscopy. In addition, patients with outflow obstruction (e.g., müllerian anomalies) have a significantly increased risk of endometriosis.
 - b. **Experimental evidence.** Endometrial fragments from menstrual fluid can grow both in tissue culture and after injection beneath the skin of the abdominal wall.
2. **Hematogenous or lymphatic spread.** Endometriosis at sites distant from the pelvis may be caused by vascular or lymphatic transport of endometrial fragments. This could explain the presence of endometriosis at distant sites such as the brain and lungs.
3. **Metaplasia of the coelomic epithelium.** The transformation of coelomic epithelium results from some yet-unspecified stimuli, but it can occur early in puberty after a few menstrual cycles.
4. **Genetic influences.** The relative risk of endometriosis is 7% in siblings, compared with 1% in control groups. The exact genetic transmission has yet to be determined.
5. **Immune factors.** An altered immunologic response may be involved in the pathogenesis of endometriosis. This is an active area of research and has yet to be clarified. This may explain why although many if not all women experience retrograde menstruation, not all women develop endometriosis.

- B Pain in endometriosis** There are multiple mechanisms to explain the pain observed with endometriosis.
1. Infiltrating endometriosis may cause irritation or direct invasion of pelvic floor nerves.
 2. Active bleeding from endometriotic implants may directly irritate peritoneal nerves or indirectly cause symptoms by accumulation of blood products.
 3. Pain may result from growth factors, cytokines, prostaglandins, and histamines in endometriotic tissue and peritoneal fluid of women with endometriosis. In fact, levels of these compounds may be most elevated in patients with the earlier and more atypical forms of the disease.
- C Infertility in endometriosis** Moderate to severe endometriosis is thought to cause infertility by causing adhesions and scarring of the ovaries and fallopian tubes. Whether minimal endometriosis causes infertility is still under investigation.
1. Patients with endometriosis may have increased concentrations of macrophages in the ampullary portions of the fallopian tubes. Macrophages, chemotactically attracted to areas where endometriosis is present, may interfere with ovulation and corpus luteum formation and with fertilization through gamete phagocytosis. Factors produced by macrophages may interfere with sperm motility.
 2. Prostaglandin F_{2a} increases the tone and amplitude of the cervical and uterine musculature and narrows the cervical os. It may increase the venous constriction of the uterus and the intensity of uterine contractions, therefore increasing the degree of dysmenorrhea. Prostaglandins also may interfere with placentation or implantation.
 3. Interleukins are also secreted by the activated macrophages. Exposed embryos are less likely to progress to the eight-cell stage at 24 hours. Tumor necrosis factor and other cytokines may stimulate endometrial cell proliferation.
 4. Randomized controlled trials have shown that surgical treatment of minimal and mild endometriosis at laparoscopy results in a small increase in pregnancy rates. This suggests that minimal and mild endometriosis plays a role in infertility, but how significant a role is unclear.

III

SIGNS AND SYMPTOMS

- A Dysmenorrhea** Secondary dysmenorrhea (menstrual pain secondary to an anatomic pelvic abnormality) is the most common symptom of endometriosis. Typically the pattern with endometriosis is that of increasingly severe menstrual pain over time. With the increased use of laparoscopy, many adolescents with presumed primary dysmenorrhea are being diagnosed with endometriosis.
- B Pain with ovulation** is associated with endometriosis. Unilateral pain can suggest endometriomas within the ovary.
- C Chronic pelvic pain** Pelvic pain for more than 6 months (diffuse or localized in the pelvis) is considered chronic. However, many women with endometriosis are asymptomatic, and the degree of endometriosis often does not correlate with the existing amount of pain.
- D Dyspareunia** Painful intercourse may be caused by:
1. Endometrial implants of the uterosacral ligaments
 2. Endometriomas of the ovaries
 3. Fixed retroversion of uterus and/or fixed location of ovaries in the cul-de-sac due to endometriosis and adhesions
- E Infertility** Endometriosis has been demonstrated by laparoscopy in as many as 30% to 40% of women who are infertile. Endometriosis has also been noted in fertile women undergoing tubal ligation. Therefore, it is not clear that endometriosis is the cause of infertility; there may just be an association.

F Associated symptoms

1. **Urinary.** Urinary symptoms are common in patients with endometriosis; as many as one-third of patients with endometriosis have urinary tract involvement. The highest frequency of such involvement occurs in the bladder, followed in frequency by the lower ureter, upper ureter, and kidney. Symptoms range from intermittent dysuria, frequency, and urgency to complete ureteral obstruction. Gross or microscopic hematuria is present in many patients and frequently follows the menstrual cycle. Bladder involvement can mimic symptoms of interstitial cystitis, and need to be differentiated.
2. **Gastrointestinal.** Seven to thirty-five percent of all women with endometriosis have bowel involvement. Symptoms may vary from dyschezia (pain on defecation) and hematochezia (bloody bowel movements, in this case associated with menstruation) to other symptoms of partial or complete bowel obstruction (e.g., abdominal bloating, intestinal cramps, nausea, and vomiting). Although severe cases of bowel involvement may be diagnosed by magnetic resonance imaging (MRI) or computed tomography (CT), the most practical method of diagnosis remains a radiographic evaluation of the bowel with barium contrast. Because endometriosis induces **severe inflammation** in the serosa, muscularis, and mucosa of the bowel, a “**tethering effect**” is often apparent on a barium enema or upper gastrointestinal series. This can be missed with a colonoscopy. Symptoms from endometriosis can be similar to those of other gastrointestinal diseases such as irritable bowel and inflammatory bowel disease.

G Distant sites for endometriosis

1. **Thoracic.** The thorax is a rare but significant site of endometriosis. The foci of endometriosis can cause cyclic monthly pneumothorax (catamenial pneumothorax), hemoptysis, or hemothorax. The onset of chest pain usually occurs within 2 days of menses. Initial management usually involves hormonal management as outlined below. However, if medical management is unsuccessful, more aggressive measures such as thoracoscopy with pleurodesis may be necessary. Pleurodesis will likely be effective at preventing pneumothorax and hemothorax, but because the implants of endometriosis may still be present, catamenial chest pain may still occur.
2. **Other.** Endometriosis has been documented to occur in other distant sites including nasal passages (monthly nose bleeds), the brain (catamenial seizures), and the umbilicus. Endometriosis can also occur in surgical incisions, typically laparotomy from cesarean sections or surgery for endometriosis, and in laparoscopy port sites. For this reason it is important to not remove endometriotic tissue directly through the skin incisions.

H Differential diagnosis When considering the diagnosis of endometriosis, one must exclude other conditions or diseases that can cause the same symptoms. At the same time, it is important to consider these other causes of pain in a patient who is not responding to treatment for endometriosis.

1. **Gynecologic causes**
 - a. Ovarian cysts
 - b. Müllerian anomalies
 - c. Pelvic inflammatory disease (PID) and sexually transmitted diseases
 - d. Malignancy
2. **Urinary system**
 - a. Interstitial cystitis
 - b. Kidney stones
3. **Musculoskeletal system**
 - a. Trigger point pain
 - b. Pelvic floor dysfunction
4. **Gastrointestinal system**
 - a. Irritable bowel disease
 - b. Inflammatory bowel disease

IV

DIAGNOSIS

History and physical examination may be suggestive of endometriosis, but currently the only way to diagnose the condition is by visualization at surgery (usually laparoscopy) or by biopsy of implants.

A History The patient might have one or more of the characteristic symptoms (see III). A history of endometriosis in the patient's mother or sister is also important.

B Markers for endometriosis

1. **CA-125 is elevated** in endometriosis. The CA-125 assay is a test for cell surface antigen found on coelomic epithelium, which includes the endometrium. This test is useful as a marker for response to treatment or recurrence. **CA-125 is not a diagnostic test for endometriosis because it lacks specificity.** It can also be elevated in ovarian cancer, PID, and inflammatory bowel disease.

C Pelvic examination

1. **Nodularity and tenderness of the uterosacral ligaments** are characteristic findings on vaginal and/or rectovaginal examination.
2. **Endometriomas** (ovarian cysts filled with old blood from endometriosis, forming “**chocolate cysts**”) are palpated as adnexal masses often fixed to the lateral pelvic walls or to the posterior cul-de-sac.
3. The uterus is often in a **fixed retroverted** position.
4. The pelvic examination in minimal endometriosis is usually normal.

D Pelvic imaging is necessary in a woman with pelvic pain in whom endometriosis is suspected in order to look for ovarian endometriomas. Pelvic ultrasound is the best screening tool for visualizing the ovaries and uterus. MRI is better for clarifying the findings on ultrasound. On MRI endometriomas are typically hyperintense in T1 imaging and hypointense on T2 imaging. CT scan is not helpful for diagnosing endometriomas. Typical endometriotic lesions are not visualized with pelvic ultrasound or even with MRI. In adolescents with severe dysmenorrhea, pelvic ultrasound should be performed to look for obstructive müllerian anomalies such as a blind noncommunicating uterine horn or a hemi-obstructed vagina with a uterus didelphys.

E Laparoscopy and the classification of endometriosis Laparoscopy is necessary for the diagnosis of endometriosis. A laparoscopy is indicated to look for endometriosis or other causes of pelvic pain if the woman has failed to respond to medical therapy or if there is an abnormality seen on pelvic imaging suggesting endometriosis.

1. Appearance

- a. The classic endometriotic implant is characterized as brown or black pigmentation (**powder-burn lesion**) and fibrosis.
 - b. Lesions that are **clear vesicular, white opacified, glandular excrescences, polypoid, or red hemorrhagic vesicles** are considered to be “atypical” lesions of endometriosis. Studies also suggest that these implants may be the most metabolically active. These lesions represent the majority of endometriosis seen in adolescents. It is not clear whether these lesions represent a different form of endometriosis or are a precursor to the typical lesions.
 - c. White scarring of pelvic peritoneum suggests old burned-out endometriosis.
2. Endometriosis may cause deep tissue damage, resulting in local scarring and reduplication of **peritoneum** and leading to **surface defects** or **Allen-Masters peritoneal defects**. Physicians should strongly suspect the possibility of endometriosis in all patients with demonstrated pelvic peritoneal defects at laparoscopy.
 3. **Classification.** The extent of formation of classic lesions, ovarian involvement, and adhesive disease is classified by the American Society of Reproductive Medicine. Classically severity of endometriosis is graded by stages I through IV corresponding to minimal, mild, moderate, and severe disease respectively.

V

TREATMENT

A General considerations Age of the patient, extent of disease, duration of the infertility, and severity of symptoms are important considerations. The patient's reproductive plans should also be taken into account. Prior to initiating medical treatment for endometriosis, it is important to have made the correct diagnosis by the modalities noted above including laparoscopy and to consider and exclude other causes of the patient's symptoms.

B Expectant treatment

1. Expectant therapy may be appropriate in young women who have mild pelvic pain with apparent endometriosis on laparoscopy and no immediate interest in pregnancy. Goals are relief of the dysmenorrhea and prevention of further growth of endometriosis.
 - a. **Nonsteroidal anti-inflammatory drugs (NSAIDs).** The prostaglandin synthetase inhibitors are effective in controlling endometriosis-related dysmenorrhea. Women with endometriosis show increased concentrations of prostaglandins in the peritoneal fluid. When oral contraceptive pills (OCPs) and NSAIDs are administered simultaneously, they have a synergistic effect.
2. Women with minimal disease and short-term infertility may be managed expectantly, but fertility may be an issue. Recent data have shown that conservative surgery (laparoscopic treatment of endometriosis) is superior to expectant management in achieving fertility in the next year.

C Medical therapy Ectopic endometrium responds to cyclic hormone secretion in a fashion similar to normal endometrium. It has been well documented that pregnancy tends to alleviate the symptoms of endometriosis. It was this observation that led to the initiation of **hormonal suppression of menses as the basis of medical therapy for endometriosis**. Newer therapies have focused on the specific hormonal triggers for endometriosis. Medical therapy is not indicated for treatment of infertility related to endometriosis, as there is no proven benefit and therapy delays attempting pregnancy.

1. **Combined oral contraceptive pills.** This is usually the first-line therapy for endometriosis and can be administered in the traditional cyclic fashion allowing menstruation or administered continuously to prevent menstruation.
 - a. **Mode of action.** Continuously administered estrogen–progestin combination OCPs create a “pseudopregnancy” state associated with amenorrhea. The pseudopregnancy causes decidualization, necrobiosis, and resorption of the ectopic endometrium. This treatment is appropriate to control pain associated with menstruation and ovulation with endometriosis. Transdermal and vaginal hormonal contraceptives can be used in the same way as oral preparations.
 - b. **Dosage.** Hormonal contraceptive pills can be used with estrogen doses of 20 to 35 µg. They are given daily with the placebo pills given every 4 to 12 months to induce withdrawal bleeding. Addition of conjugated estrogens for short periods controls breakthrough bleeding.
 - c. **Prognosis.** The recurrence rate of pain symptoms is 15% to 25% in the following year.
2. **Progestins**
 - a. **Mode of action.** Progestins can be given alone for treatment of endometriosis by suppressing ovulation and therefore inducing amenorrhea. They cause anovulation by enhancing the negative feedback of estrogen at the hypothalamus leading to a hypogonadotropic hypoestrogenic state. Progestins also have an antimitotic effect on endometrial tissue within the uterus (the eutopic endometrium as well as in endometrial implants). This results in eventual atrophy of endometrial implants.
 - b. **Administration/dosage.** Progestins may be administered through several routes.
 - (1) **Oral**—norethindrone acetate 5 mg daily for 2 weeks, increasing by 2.5 mg every 2 weeks to maximum dose of 15 mg daily. The dose used is the lowest effective dose to achieve amenorrhea, and should be continued while symptoms are controlled.
 - (2) **Injection**—depot medroxyprogesterone acetate (104 mg subcutaneous injection or 150 mg intramuscular preparation) every 12 to 14 weeks. This agent has been associated with increased risk of osteoporosis and decrease in bone density with prolonged use; therefore, it is advised to restrict its use to less than 2 years. Of note, compared to gonadotropin-releasing hormone (GnRH) agonists, the effect on bone is less severe allowing this therapy to be continued for longer periods of time than GnRH agonists.

(3) **Intrauterine**—levonorgestrel-releasing intrauterine device (LNG IUD) delivers a steady rate of 20 µg daily of levonorgestrel into the uterine cavity causing local atrophy of the endometrium; therefore, the systemic levels of progestin is less than for oral or injectable administration. Therefore, side effects such as weight gain, breast tenderness, bloating, etc., are reduced with this route of administration.

c. **Prognosis.** The agents have been reported to decrease the pain associated with endometriosis in up to 80% of patients. Unfortunately, breakthrough spotting/bleeding is a troublesome side effect of all these agents, which is the main reason for many patients to discontinue these medications.

3. GnRH agonists

a. **Mode of action.** GnRH is a decapeptide that controls the release of the anterior pituitary hormones (follicle-stimulating hormone [FSH] and luteinizing hormone [LH]). GnRH has a very short half-life; it is rapidly destroyed by endopeptidases in the hypothalamus and pituitary gland. Release of native GnRH from the hypothalamus is pulsatile to achieve stimulation from the pituitary. Continuous release of GnRH would result in downregulation and suppression of pituitary hormone secretion. Chemical alterations of the amino acids at positions 6 and 10 produce synthetic derivatives of GnRH (GnRH analogs, GnRH agonists) that resist cleavage by endopeptidases but retain a high affinity for the pituitary GnRH receptor. The effect is **downregulation** and **desensitization** of the pituitary with resulting lack of ovarian estrogen production.

b. **Administration.** GnRH agonists may be administered daily as intranasal or subcutaneous administration or as a depot injection every month or every 3 months.

c. **Adverse effects** are related primarily to the hypoestrogenic state induced by GnRH agonists.

(1) Menopausal-type symptoms (e.g., hot flashes, decreased libido, vaginal dryness, and headaches) occur because of the hypoestrogenic state.

(2) Prolonged use (more than 6 months) may result in significant bone loss as a result of the hypoestrogenic state that is not reversible. Using “**add-back therapy**” (low-dose estrogen and progestin, or norethindrone acetate 5 mg daily) may minimize bone loss and vasomotor symptoms while still maintaining pain relief. Oral contraceptives are not used as add-back therapy.

(3) Flare-ups of endometriotic symptoms may occur in the first few weeks after treatment begins because of the initial temporary rise in estrogen levels after starting GnRH agonists. These symptoms typically abate. GnRH antagonists may have a role in initial suppression in these patients.

d. **Prognosis.** Amenorrhea and atrophic endometrial changes occur in most patients. Regression of endometriotic lesions occurs in 80% of cases, and symptomatic relief occurs in more than 50% of cases after 6 months of therapy. However, recurrence rates are 25% to 30% per year after therapy is discontinued.

4. Danazol

a. **Mode of action.** Danazol is an androgenic testosterone derivative that suppresses FSH and LH resulting in reduction of ovarian estrogen and progesterone production. Danazol also directly acts on endometrial glands to produce an atrophic (thin) endometrium.

b. **Dosage.** Danazol is administered as 200 mg four times daily for 4 to 9 months. The dose may be lowered to 100 to 600 mg/d after the onset of amenorrhea.

c. **Prognosis.** Eighty to ninety percent of patients will have clinical improvement on danazol, but significant androgenic side effects such as hirsutism, acne, weight gain, and decreased breast size have limited its use today given the availability of better tolerated therapies.

5. Aromatase inhibitors

a. **Mode of action.** The aromatase enzyme converts androgen precursors such as androstenedione and testosterone to estrone and estradiol. Aromatase inhibitors such as letrozole and anastrozole will inhibit the production of estrogen within the endometriotic lesion. These medications will increase FSH and LH by blocking estrogen’s negative feedback on the pituitary. These elevated gonadotropins will stimulate ovarian follicular development unless there is concomitant use of progestins, low-dose OCPs, or GnRH agonists. Aromatase inhibitors are currently indicated for the treatment of breast cancer and their use in endometriosis, while promising, should be considered investigational at this point in time.

- b. **Dosage.** Studies have used 2.5 mg of letrozole or 1 mg of anastrozole per day in conjunction with ovarian suppressive therapy with progestin's, OCPs, or GnRH agonists. Therapy continues for 6 to 9 months.
- c. **Adverse effects.** Side effects of aromatase inhibitors are usually benign and include nausea, diarrhea, and headache. Hot flashes are milder and infrequent when compared to GnRH agonists. However, because of the profound reduction in estrogen levels, long-term use carries the risk of bone loss. Concurrent treatment with OCPs or progestins can mitigate this bone loss.
- d. **Prognosis.** Initial small clinical studies have shown approximately 90% pain relief after treatment with anastrozole or letrozole.

D Surgical therapy Medical therapy does not treat adhesions or eliminate endometriomas. Surgery is the treatment of choice in cases that present with considerable anatomic factors (e.g., adhesions, endometriomas, ureteral obstruction). The success of surgery in relieving infertility is directly related to the severity of the endometriosis.

1. **Conservative surgery** involves the excision, fulguration, or laser vaporization of endometriotic lesions; the excision of ovarian endometriomas; and the resection of severely involved viscera, leaving the uterus and at least one ovary and fallopian tube intact. This can usually be accomplished by laparoscopy, but in severe cases laparotomy may be required. Studies have shown that gentle micromanipulation of the tissue, lysis of adhesions, and meticulous hemostasis are important in the patient desiring fertility. Unfortunately, pain often recurs after conservative surgery and the risk of recurrence varies with the severity of the disease. Recurrence of symptoms 7 years after conservative surgery was noted in 37% of patients with mild disease and 74% of patients with severe disease.
2. **Radical surgery** involves a total hysterectomy and bilateral salpingo-oophorectomy.
 - a. This approach is used in patients who do not desire future fertility or in those whose endometriosis is so severe that it precludes any attempt at reconstruction.
 - b. The rate of reoperation on women who have a hysterectomy with the ovaries left in place is high. In women with endometriosis who underwent hysterectomy with preservation of ovaries and were followed for a mean of 58 months, 62% had recurrence of symptoms and 31% underwent repeat surgery. In women who had bilateral salpingo-oophorectomy with hysterectomy, the symptom recurrence rate was 10% and reoperation rate was 4%. Therefore, patients who have their ovaries retained were six times more likely to have recurrence of pain and eight times more likely to need subsequent surgery. This risk may be acceptable for some women who would rather not experience surgical menopause at a young age.
 - c. **Estrogen replacement therapy** is important in patients who undergo radical surgery to prevent osteoporosis and treat hypoestrogenic symptoms such as hot flushes, night sweats, sleeplessness, and vaginal dryness. Estrogen replacement therapy carries only a small risk of inciting growth of residual endometriosis. In some women, addition of progestin may be advised to suppress growth of endometriotic lesions.



Study Questions for Chapter 27

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A 15-year-old girl, gravida 0, para 0, presents with a history of severe midline lower abdominal pain associated with her periods since the age of 12 years. Vaginal examination is not performed because the patient is still virginal. An abdominal ultrasound reveals normal pelvic anatomy. The patient's mother and two older sisters have a history of endometriosis. She has tried NSAIDs and oral contraceptive pills to control her pain but neither has helped. What is the next step in your management?

- ☐ A Expectant management
- ☐ B Subcutaneous medroxyprogesterone
- ☐ C Diagnostic laparoscopy
- ☐ D GnRH agonist
- ☐ E Aromatase inhibitor with oral contraceptive pills

2. A 38-year-old woman, gravida 3, para 3, undergoes a laparoscopy and bilateral tubal ligation. During her laparoscopy, you find incidentally that she has endometriotic lesions on her uterosacral ligaments and the peritoneum overlying her bladder. She is not consented for fulguration of her endometriosis; therefore, you only perform her tubal ligation. She comes to your office for her postoperative visit. She has no symptoms from her endometriosis. Your next step in her management is:

- ☐ A Expectant management
- ☐ B Oral contraceptive pills
- ☐ C Laparoscopy with fulguration of endometriotic implants
- ☐ D Danazol
- ☐ E GnRH agonist

3. A 29-year-old woman, gravida 0, para 0, presents with 2-year history of cyclic pelvic pain. She has been taking birth control pills continuously. Her pelvic examination is significant for a right adnexal mass. A recent pelvic ultrasound reveals a 7-cm right complex ovarian mass. You perform a laparoscopy and find that she has a right endometrioma and several deep endometriotic lesions on both uterosacral ligaments. A right ovarian cystectomy is performed and laser ablation of the endometriotic implants. Patient does not desire fertility at present. She continues to take her birth control pills continuously for 6 months but then her symptoms return. What is the next step in management?

- ☐ A Diagnostic laparoscopy
- ☐ B Pelvic ultrasound
- ☐ C GnRH agonist
- ☐ D Total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO)
- ☐ E Danazol

4. A 32-year-old female, gravida 1, para 1, presents with worsening pelvic pain with her period. She reports that her previous providers told her she likely has endometriosis based upon a longstanding history of dysmenorrhea but lately her pain is worse. She also complains of left-sided pain with intercourse and when she is jogging. She is sexually active with a single partner and uses condoms for birth control. She has had no prior surgeries and no other medical problems. On physical examination she is afebrile, has a nontender abdomen but on pelvic examination, has an enlarged left adnexal mass that is approximately 5 cm and is mildly tender to palpation. The next appropriate step is:

- ☐ A Begin empiric treatment with oral contraceptive pills
- ☐ B Obtain a pelvic ultrasound to evaluate the pelvis
- ☐ C Begin a trial of GnRH agonist to suppress estrogen production
- ☐ D Perform a laparoscopy to assess and treat the left adnexal mass
- ☐ E Perform an MRI of the pelvis

5. A 44-year-old G3P3 female presents with severe pelvic pain. Her history is notable for a laparoscopy 3 years ago for severe endometriosis requiring laser ablation of endometriosis on her uterosacral ligaments, dissection of pelvic adhesions and excision of a 4-cm endometrioma from her left ovary. She had been managed by GnRH agonist therapy for 4 months postoperatively followed by continuous oral contraceptive pill use. She had initial relief of symptoms; however, she is now bothered by daily pain, dyspareunia, and dyschezia. Pelvic examination reveals a fixed retroverted uterus and bilateral uterosacral ligament nodularity. A pelvic ultrasound shows a normal uterus and right ovary and a 3-cm homogenous echogenic cyst consistent with an endometrioma of the left ovary. She does not desire future childbearing and desires the most effective therapy to relieve the pain. The most appropriate management is:

- ☐ A Danazol, 200 mg four times daily
- ☐ B Total abdominal hysterectomy (TAH)
- ☐ C GnRH agonist therapy for 6 months with norethindrone add-back
- ☐ D Laparoscopic left ovarian cystectomy
- ☐ E Total abdominal hysterectomy bilateral salpingo-oophorectomy (TAH/BSO)

QUESTIONS 6–9

Match the statement below with the best word or words above. Each answer choice may be used once, more than once, or not at all.

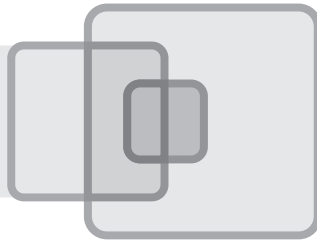
- ☐ A Norethindrone acetate
- ☐ B Endometrioma
- ☐ C Combined hormonal contraception
- ☐ D Hematochezia
- ☐ E Aromatase inhibitors

- 6. Block production of estrogen within the endometriosis implant.
- 7. To ameliorate the menopausal symptoms of GnRH agonist therapy.
- 8. Ovarian cysts filled with old blood from endometriosis.
- 9. Complication of extraperitoneal endometriosis.



Answers and Explanations

1. **The answer is C** [IV C]. The patient is experiencing severe symptoms so expectant management is not an option. Adolescents younger than age 18 who have failed NSAIDs and OCP therapy should be offered a diagnostic laparoscopy to confirm the diagnosis of endometriosis and to treat the disease surgically if noted at that time. As both subcutaneous medroxyprogesterone and GnRH agonists decrease bone density, these are not suitable options for an adolescent patient younger than age 18 who does not have a definitive diagnosis of endometriosis. Once endometriosis has been diagnosed, either of these medications may be considered if the benefits are felt to outweigh the risks. Aromatase inhibitor with oral contraceptive pills has not been studied in the adolescent population and its use is still mainly investigational.
2. **The answer is A** [V B]. This patient has asymptomatic endometriosis and she has completed her childbearing; therefore, she does not require any treatment at present. Endometriosis may be encountered incidentally in up to 20% of patients who are asymptomatic and are having a procedure for another indication.
3. **The answer is B** [V C 3]. This patient has severe endometriosis. Despite undergoing surgical management and continuous OCP therapy her symptoms have returned. The patient underwent surgery 6 months ago, therefore performing another laparoscopy will unlikely reveal any surgically amenable endometriotic lesion. A pelvic ultrasound will not be helpful in this situation as it will likely be normal after her recent surgical management. GnRH agonist would be the most suitable next step for this patient to help with her symptoms and it is preferable to danazol as the latter has many androgenic side effects. Use of concomitant progestin therapy with the GnRH agonist will reduce hypoestrogenic side effects and decrease bone loss. A TAH-BSO is too radical for a young reproductive age woman.
4. **The answer is B** [IV D]. It is important to evaluate for other causes of pelvic pain in reproductive age women. When pain and a pelvic mass are present, it is imperative to further characterize the mass. Ultrasound will distinguish between a follicular or “functional” cyst that can be followed expectantly, and a complex cyst that may represent a tumor or endometrioma. If further clarification is needed, an MRI can be performed; however, the use of MRI for initial evaluation is not cost effective in most circumstances. Because the 5-cm mass in this case could represent a functional cyst, immediate laparoscopy is not warranted. Empiric treatment with birth control pills in patients with dysmenorrhea and a normal examination can be considered but it is unwise to do this in the presence of an adnexal mass because of the risk of neoplasm. The risk of neoplasm also precludes initial treatment with a GnRH agonist.
5. **The answer is E** [V D 2]. This patient has severe recurrent endometriosis. The most effective therapy is TAH/BSO. Unfortunately, recurrence of symptoms is common with both medical and surgical treatment of endometriosis. Up to 50% of patients with uterine sparing surgery will have recurrence of symptoms within 5 years. A hysterectomy is significantly more likely to be effective if the ovaries are removed with the uterus. Retention of the ovaries confers a sixfold risk of recurrence of pain. A laparoscopic ovarian cystectomy will likely only provide temporary relief. GnRH agonist therapy may provide temporary relief but is unlikely to provide a long-term solution. Danazol is unlikely to be more effective than birth control pills and has more androgenic side effects.
6. **E, 7. A, 8. B, 9. D.** Aromatase inhibitors block conversion of testosterone to estrogen within the endometriotic lesion. Norethindrone, a synthetic progestin, is commonly used as “add-back therapy” to help with troublesome menopausal type symptoms and minimizing bone loss. Endometriomas are all called chocolate cysts due to the characteristic contents of old blood. Endometriosis within the colonic mucosa is extraperitoneal and causes bleeding from the rectum with menses.



Uterine Leiomyomas

LAXMI A. KONDAPALLI • MONICA A. MAINIGI

I

INTRODUCTION

Uterine leiomyomas, which are also known as myomas, fibroids, or fibromyomas, are proliferative, well-circumscribed, pseudoencapsulated, benign tumors composed of smooth muscle and fibrous connective tissue.

- A** Leiomyomas are the **most common uterine mass** and the most common neoplasm found in the female pelvis. They are present in 20% to 40% of women of 35 years of age or older, and rarely can be present in adolescents.
- B** They vary in diameter from 1 mm to more than 20 cm.
- C** Leiomyomas may be single but most often are multiple; 100 or more have been found in a single uterus.

II

ETIOLOGY

Leiomyomas are benign neoplasms that arise from uterine smooth muscle. These smooth muscle tumors may be found in organs outside the uterus, including the fallopian tubes, vagina, round ligament, uterosacral ligaments, vulva, and gastrointestinal tract.

- A** **Cytogenetic studies** suggest that leiomyomas arise from a single neoplastic smooth muscle cell; in other words, they are **monoclonal** tumors resulting from somatic mutations. A variety of chromosomal abnormalities involving chromosomes 6, 7, 12, and 14 have been identified, suggesting a genetic role in the pathogenesis of these tumors. Disruption or dysregulation of the high mobility group genes on chromosome 12 appears to contribute to fibroid development.
- B** **Hormones** affect growth of leiomyomas but do not appear to be the cause. Evidence that suggests that estrogen is a promoter of leiomyoma growth includes:
 1. Leiomyomas are rarely found before puberty and stop growing after menopause.
 2. New leiomyomas rarely appear after menopause.
 3. Leiomyomas often grow rapidly during pregnancy.
 4. Gonadotropin-releasing hormone (GnRH) agonists create a hypoestrogenic environment that results in a reduction of the size of leiomyomas. This effect is reversible on cessation of treatment.
- C** **Local and paracrine factors**, such as blood supply and proximity to other tumors, may account for variations in tumor volume and rate of growth. In addition, some peptide growth factors may play an etiologic role.
 1. Epidermal growth factor (EGF) induces DNA synthesis in leiomyomas and myometrial cells.
 2. Estrogen may exert its effect through EGF.
 3. Recent studies in animals have shown that pirfenidone, an antifibrotic agent, suppresses leiomyoma growth via its potent inhibition of fibrogenic cytokines, including basic fibroblast growth factor, platelet-derived growth factor, transforming growth factor- β , and EGF.

III

CLASSIFICATION AND PATHOLOGY

A **Classification of leiomyomas according to location** (Fig. 28–1). Three types of leiomyomas occur on the basis of their location within or on the uterus.

1. **Intramural leiomyomas** are the most common variety, occurring within the myometrium of the uterus as isolated, encapsulated nodules of varying size. As these tumors grow, they can distort the uterine cavity or the external surface of the uterus. These tumors can also cause symmetric enlargement of the uterus when they occur singly.
2. **Submucosal leiomyomas** are located beneath the endometrium and can grow into the uterine cavity. They can be **pedunculated** (i.e., attached to the endometrium by a stalk) and may protrude to or through the cervical os into the vagina. These tumors are often associated with abnormal bleeding and menorrhagia severe enough to cause significant anemia.
3. **Subserosal leiomyomas** are located just beneath the serosal surface and grow out toward the peritoneal cavity, causing distortion of the peritoneal surface of the uterus. When leiomyomas extend into the broad ligament, they are known as **intraligamentary leiomyomas**. These tumors may become pedunculated, and reach a large size within the peritoneal cavity without producing symptoms. These potentially mobile tumors may present in such a manner that they need to be differentiated from solid adnexal lesions. Pedunculated leiomyomas may also attach themselves to an adjacent structure such as the omentum, mesentery, or bowel; develop a secondary blood supply; and lose their connection with the uterus and primary blood supply. This situation occurs rarely, and the resulting structures are known as **parasitic leiomyomas**.

B **Pathology**

1. **Gross pathology.** Leiomyomas are **pseudoencapsulated** solid tumors, well demarcated from the surrounding myometrium. The **pseudocapsule** is not a true capsule and results from compression of fibrous and muscular tissue on the surface of the tumor. Because the vasculature is located on the periphery, the central part of the tumor is susceptible to degenerative changes and necrosis. The tumors are smooth, solid, and usually pinkish-white, depending on the degree of vascularity. The surface typically has a trabeculate, fleshy, whorl-like appearance.

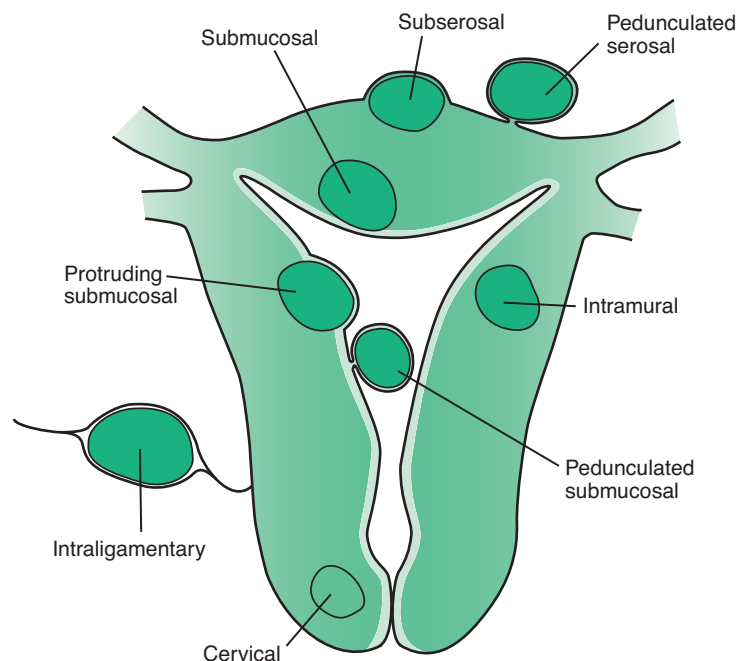


FIGURE 28–1 Uterine myomata.

2. **Microscopic pathology.** Leiomyomas are composed of groups and bundles of smooth muscle fibers in a twisted, whorled fashion. Microscopically, these appear as smooth muscle cells in longitudinal or cross-section intermixed with fibrous connective tissue. Vascular structures are few, and mitoses are rare.
 - a. **Cellular leiomyomas** are tumors with mitotic counts of 5 to 10 per 10 consecutive high-power fields that lack cytologic atypia. These are not considered cancerous.
 - b. **Leiomyosarcomas** are a distinct clinical entity and are diagnosed on the basis of a **mitotic count** of 10 mitotic figures per 10 high-power fields. These malignant tumors are found rarely in hysterectomy or myomectomy **specimens** (incidence 0.2%). Recently, the importance of other factors with respect to malignant potential, such as **cellular atypia** and **coagulative necrosis** of tumor cells, has been recognized.

C Degenerative changes A variety of degenerative changes may occur in leiomyomas that alter the gross and microscopic appearance of the tumors. Most of these changes have no clinical significance. Degenerative changes occur secondary to alterations in circulation (either arterial or venous), postmenopausal atrophy, or infection, or they may result from malignant transformation.

1. **Hyaline degeneration**, the most common type of degeneration, is present in almost all leiomyomas. It is caused by an overgrowth of the fibrous elements, which leads to a hyalinization of the fibrous tissue and, eventually, calcification.
2. **Cystic degeneration** may occasionally be a sequel of necrosis, but cystic cavities are usually a result of myxomatous change and liquefaction after hyaline degeneration.
3. **Necrosis** is commonly caused by impairment of the blood supply or severe infection. A specific kind of necrosis is the **red**, or **carneous**, degeneration, which occurs most frequently in pregnancy. The lesion has a dull, reddish hue and is believed to be caused by aseptic degeneration associated with local hemolysis.
4. **Mucoid degeneration** may occur when the arterial input is impaired, particularly in large tumors. Areas of hyalinization may convert to a mucoid or myxomatous type of degeneration; the lesion has a soft, gelatinous consistency. Further degeneration can lead to liquefaction and cystic degeneration.
5. **Infection** of a leiomyoma most commonly occurs with a pedunculated submucosal leiomyoma that first becomes necrotic and then becomes infected.
6. **Calcification** of leiomyomas is a common finding in postmenopausal patients.
7. **Sarcomatous degeneration** occurs in less than 1% (0.13% to 0.29%) of leiomyomas. Whether this represents a true degenerative change or a spontaneous neoplasm is a subject of controversy. The presence of a leiomyosarcoma within the core of an apparently benign pseudoencapsulated leiomyoma suggests such a degenerative process. This type of sarcoma is usually of a spindle cell rather than a round cell type. The 5-year survival rate for patients with a leiomyosarcoma arising within a leiomyoma is much better than that for a true leiomyosarcoma of the uterus with extension of the sarcomatous tissue beyond the pseudocapsule of the leiomyoma.

IV

ASSOCIATED SYMPTOMS AND SIGNS

A Symptoms These vary greatly, depending on size, number, and location of the leiomyoma or leiomyomas. Most women with leiomyomas are asymptomatic; symptoms occur in 10% to 40% of patients.

1. **Abnormal uterine bleeding.** This is the most common symptom associated with uterine leiomyomas, occurring in as many as 30% of symptomatic women. The typical bleeding pattern is **menorrhagia**, or excessive bleeding at the time of menses (more than 80 mL). The increase in flow usually occurs gradually, but the bleeding may result in a profound anemia. The exact mechanisms of increased blood loss are unclear. Possible factors include necrosis of the surface endometrium overlying the submucosal leiomyoma, a disturbance in the hemostatic contraction of normal muscle bundles when extensive intramural myomatous growth occurs, an increase in surface area of the endometrial cavity, or an alteration in endometrial microvasculature. In some cases, abnormal bleeding may be associated with anovulatory states. Leiomyomas can be

associated with polyps and endometrial hyperplasia, which may produce an abnormal bleeding pattern. Endometrial sampling is advised if abnormal bleeding is present.

2. **Pain.** Uncomplicated uterine leiomyomas usually do not produce pain. Acute pain associated with fibroids is usually caused by either torsion of a pedunculated leiomyoma or infarction progressing to carneous degeneration within a leiomyoma. Pain is often crampy with a submucosal leiomyoma within the endometrial cavity, and severe cramping can occur as the uterus contracts to try to “deliver” the fibroid through the cervical os.
3. **Pressure.** As leiomyomas enlarge, they may cause a feeling of pelvic heaviness or produce pressure symptoms on surrounding structures.
 - a. **Urinary frequency** is a common symptom when a growing leiomyoma exerts pressure on the bladder.
 - b. **Urinary retention**, a rare occurrence, can result when myomatous growth creates a fixed, retroverted uterus that pushes the cervix anteriorly under the symphysis pubis in the area of the posterior urethrovesicular angle.
 - c. **Unilateral ureteral obstruction** can be caused by lateral extension or intraligamentous leiomyomas. A markedly enlarged uterus that extends above the pelvic brim may cause ureteral compression, hydronephrosis, and hydronephrosis.
 - d. **Constipation and difficult defecation** can be caused by large posterior leiomyomas.
 - e. **Compression of pelvic vasculature** by a markedly enlarged uterus may cause varicosities or edema of the lower extremities. Compression of pelvic vessels can lead to the development of deep venous thrombosis within the pelvis and pulmonary embolus.
4. **Reproductive disorders.** Infertility due to leiomyomas is probably uncommon. Infertility may result when leiomyomas interfere with normal tubal transport or implantation of the fertilized ovum.
 - a. **Large intramural leiomyomas located in the cornual regions** may virtually close the interstitial portion of the tube and predispose to ectopic pregnancy.
 - b. **Submucosal leiomyomas** may impede implantation if larger than 4 to 5 cm; the endometrium overlying the leiomyoma may be out of phase with the normal endometrium and thus provide a poor surface for implantation.
 - c. **Increased incidences of abortion and premature labor** occur in patients with submucosal leiomyomas.
 - d. Less successful results with in vitro fertilization occur in patients who have submucosal fibroids when compared to controls.
5. **Pregnancy-related disorders.** Uterine leiomyomas, found in 0.3% to 7.2% of pregnancies, are usually present before conception and may increase in size significantly during gestation.
 - a. Although women with leiomyomas have a higher **incidence of spontaneous abortion**, the tumors are an uncommon cause of abortion.
 - b. **Red degeneration** is occasionally observed in late pregnancy. This condition is due to central hemorrhagic infarction and the key symptom is pain. It may also be associated with nausea, vomiting, rebound tenderness, mild fever, and leukocytosis. This condition must be distinguished from other causes of abdominal pain in pregnancy because treatment is conservative with rest, analgesia, and observation. Surgical intervention is rarely, if ever, indicated.
 - c. **Preterm labor** may be increased in women with leiomyomas. The risk of preterm labor increases with the size of the fibroid.
 - d. In the third trimester, leiomyomas may be a factor in **malpresentation, mechanical obstruction, or uterine dystocia**. Large leiomyomas in the lower uterine segment may prevent descent of the presenting part. Intramural leiomyomas may interfere with effectual uterine contractions and normal labor. Cesarean section may be necessary for delivery.
 - e. **Postpartum hemorrhage** is more common with uterine leiomyomas.

B Signs

1. **Physical examination.** The diagnosis of uterine leiomyomas can be made with confidence in 95% of cases based on physical examination alone. Uterine size is defined as the equivalent gestational size as determined by abdominal and pelvic examination.

- a. **Abdominal examination.** Uterine leiomyomas may be palpated as irregular, nodular tumors protruding against the anterior abdominal wall. Leiomyomas are usually firm on palpation; softness or tenderness suggests the presence of edema, sarcoma, pregnancy, or degenerative changes.
 - b. **Pelvic examination.** The most common finding is uterine enlargement. The shape of the uterus is usually asymmetric and irregular in outline. The uterus is usually freely movable unless concomitant pelvic disease exists such as endometriosis or pelvic adhesions.
 - (1) In the case of **submucosal leiomyomas**, the uterine enlargement is usually symmetric.
 - (2) Some **subserous leiomyomas** may be distinct from the main body of the uterus and may move freely, which can be confused with adnexal or extrapelvic tumors.
 - (3) The **diagnosis of cervical leiomyomas or pedunculated submucosal leiomyomas** may be made on examination if the tumor extends through the cervical canal and into the vagina. Occasionally, a submucosal leiomyoma may be visible at the introitus.
2. **Laboratory evaluation and diagnostic studies.** Additional diagnostic studies are based on individual presentation and physical examination. In asymptomatic patients with physical examinations consistent with leiomyomas, it is not necessary to obtain additional studies routinely.
- a. **Hemoglobin and hematocrit** are obtained in cases of excessive vaginal bleeding to assess the degree of anemia and adequacy of replacement.
 - b. **Coagulation profile and bleeding time** are recommended when the history is suggestive of a bleeding diathesis.
 - c. **Endometrial biopsy** is performed in patients with abnormal uterine bleeding who are thought to be anovulatory or at increased risk for endometrial hyperplasia.
 - d. **Ultrasonography** may be used to assess uterine dimension, leiomyoma location, interval growth, and adnexal anatomy.
 - (1) Routine ultrasonography does not improve long-term outcome compared with clinical assessment alone. Pelvic ultrasound is appropriate in situations when clinical assessment is difficult or uncertain; when physical examination is suboptimal, as in cases of morbid obesity; or when adnexal pathology cannot be excluded on physical examination alone. Ultrasonography may be used to detect hydroureter and hydronephrosis in the patient with marked uterine enlargement.
 - (2) **Sonohysterography** or intrauterine infusion of sterile saline at the time of ultrasound examination can identify the presence of pedunculated submucosal leiomyomas and endometrial polyps.
 - e. **Hysteroscopy or hysterosalpingography** may be used to evaluate the endometrial cavity in the evaluation of patients with uterine leiomyomas and infertility or recurrent pregnancy loss.
 - f. **Magnetic resonance imaging (MRI)** is now being used more often in diagnosing and planning treatment for uterine fibroids. MRI has been found to be more effective than ultrasound in demarcating individual myomas, which may affect treatment, and also in assessing risk of malignancy. MRI is also better at discerning other causes of pathology including adenomyosis and adnexal masses.

V

TREATMENT

Therapy for leiomyomas must be individualized and may be nonsurgical or surgical. Treatment decisions are based on symptoms, fertility status, uterine size, and rate of uterine growth.

- A Expectant management** In the absence of pain, abnormal bleeding, pressure, or large leiomyomas, observation with periodic examination is appropriate. This is especially true if the patient is nearing menopause, at which time the leiomyomas will atrophy as estrogen levels fall.
1. **Bimanual examinations** should be performed every 3 to 6 months to determine uterine size and the rate of tumor growth. After slow growth or stable uterine size has been confirmed, annual follow-up may then be appropriate. Rapid growth—a change of 6 pregnancy weeks in size or more in 12 months or less of observation—is suspicious for malignancy and surgical intervention is indicated. Follow-up with pelvic ultrasound or MRI should be performed if physical examination is inadequate because of obesity or if it is necessary to distinguish between a fibroid and an adnexal mass.

2. **Endometrial biopsy** may be indicated in patients with **abnormal bleeding**.
3. Regular blood counts are warranted; iron deficiency anemia is common with menorrhagia, and iron replacement may be required.
4. **Nonsteroidal anti-inflammatory drugs (NSAIDs)** that inhibit prostaglandin synthesis and are administered on a scheduled rather than as-needed basis can be used to reduce menstrual blood flow. NSAIDs also treat pelvic discomfort or pressure.
5. Low-dose oral contraceptives or progestin therapy may also reduce blood loss.

B GnRH agonists Long-acting GnRH agonists suppress gonadotropin secretion and create a hypoestrogenic state similar to that observed after menopause. They are administered in the form of a subcutaneous implant or an intramuscular depot injection (administered as a monthly or every 3 months injection).

1. Although individual response varies widely, a median reduction in uterine *volume* (not diameter) of 50% has been observed with GnRH agonists. Maximum response is seen after 12 weeks of therapy, with no added advantage to 24 weeks of therapy. Decreased size is secondary to a decrease in blood flow and cell size; cell death and a decrease in cell number are not observed.
2. Leiomyomas rapidly regrow, returning to baseline size within 12 weeks after GnRH therapy is discontinued.
3. Use of GnRH agonist therapy is not recommended for longer than 24 weeks (6 months) because of the long-term effects of a hypoestrogenic state, most notably osteoporosis. Therefore, agonist therapy is often used prior to surgery to achieve a small-sized fibroid or uterus, which may impact the procedure chosen.
4. Long-term use of GnRH agonists with “add-back” hormone replacement therapy is another alternative, and can be used if the patient is a poor surgical candidate.
5. Because of potential side effects and expense, GnRH agonists are recommended for short-term use in selected cases only. For example:
 - a. For large submucosal leiomyomas to facilitate hysteroscopic resection
 - b. For leiomyomas in symptomatic perimenopausal patients who wish to avoid surgery
 - c. As presurgical treatment to decrease bleeding symptoms in patients with anemia who are taking iron in order to increase blood cell count prior to surgery

C Surgery

1. **Indications.** Surgical intervention is indicated when symptoms fail to respond to conservative management.
 - a. **Excessive bleeding** that interferes with normal lifestyle or leads to anemia and **chronic pelvic pain or pressure**.
 - b. **Protrusion** of a pedunculated submucosal leiomyoma through the cervix.
 - c. **Rapid growth** in a leiomyomatous uterus at any age. This finding warrants exploration because it may represent a leiomyosarcoma as opposed to a benign leiomyoma. Most often, leiomyosarcomas represent a distinct clinical entity rather than malignant degeneration within a leiomyoma. Because these malignancies occur primarily in women older than 40 years of age and their incidence increases with advancing age, any increase in uterine size in the postmenopausal woman warrants surgical exploration.
 - d. **Repetitive pregnancy loss caused by leiomyomas** after other etiologies has been excluded.
 - e. **Infertility patients** with leiomyomas after evaluation and treatment of other causes. The location or size of the leiomyoma should indicate that it may be a cause of the infertility.
 - f. **Enlarged uterine size** (more than 12 pregnancy weeks) in asymptomatic patients. This criterion has traditionally been cited as an indication for surgery but has recently come under scrutiny. No controlled data indicate that the proposed benefits of surgery outweigh its risks. Expectant management of asymptomatic patients with uterine enlargement of greater than 12 pregnancy weeks' size with stable or slow growth is considered a reasonable treatment option. Surgical intervention is indicated if a patient is concerned about uterine size or is symptomatic.
 - g. **Progressive hydronephrosis**, demonstrated by ultrasonography or intravenous pyelography, or **impaired renal function**.

2. **Surgical procedures.** The type of surgery to be performed depends on the age of the patient, the nature of the symptoms, the size and the location of the tumor, and the patient's desires about future fertility.
 - a. **Myomectomy** involves the removal of single or multiple leiomyomas while preserving the uterus. Myomectomy is a reasonable approach in symptomatic women unresponsive to conservative treatment who desire future fertility or uterine conservation. Eighty percent of patients report subjective improvement of symptoms, 15% of patients experience symptom recurrence, and 10% require additional treatment. The **recurrence of leiomyomas after myomectomy** depends on the number of fibroids present prior to myomectomy, race (higher in African Americans), patient age, and the completeness of the original myomectomy. Fifty percent of patients will have evidence of fibroids on ultrasound within 5 years of myomectomy. Fifteen to twenty-five percent of individuals will require further treatment for fibroids in the future.
 - (1) **Abdominal myomectomy** is performed through an incision in the abdomen with gentle dissection of the fibroids out of the uterus followed by careful uterine reconstruction. Risks of this procedure include bleeding, prolonged operative time, and increased postoperative hemorrhage compared to hysterectomy. Experienced surgeons, however, can perform myomectomy with less risk of blood loss than with hysterectomy depending on the technique used. At the time of abdominal myomectomy, it may be necessary to open the uterine cavity to remove intramural or submucosal leiomyomas completely. This is considered a risk factor for future uterine rupture and therefore is an indication for cesarean section in future pregnancies.
 - (2) **Hysteroscopic myomectomy** can be used in patients with submucosal leiomyomas and often leads to an improvement in menorrhagia. A hysteroscope is inserted transcervically into the uterine cavity and the fibroid is resected without having to enter the abdominal cavity. Criteria for hysteroscopic resection include a fibroid less than equal to 3 cm, of which at least 30% protrudes into the endometrial cavity. This procedure is associated with significantly less pain and shorter recovery periods compared to an abdominal approach. Up to 20% of women may require additional treatment within 5 to 10 years.
 - (3) Indications for **laparoscopic myomectomy** are the same as for abdominal myomectomy. Laparoscopic myomectomy may be associated with shorter recovery times, but uncertainty still exists over whether it is associated with fewer postoperative pelvic adhesions. Large, multiple, deep, and lower posterior wall leiomyomas should be approached with caution; they are technically more challenging and can be associated with a high intraoperative blood loss. Robotic-assisted laparoscopic myomectomy has advantages over traditional laparoscopic techniques due to better ease with suturing the defects in the myometrium.
 - (4) **MRI-guided focused ultrasound** is a relatively new treatment option that uses ultrasound-generated heat to cause cell death. The fibroids are localized in three dimensions with MRI, and heat from a phased array transducer is able to converge on a focal area and produce protein denaturation. An early study has shown an improvement in symptoms in nearly 60% of patients. This procedure is not widely available in the United States and ideal candidates are yet to be determined.
 - (5) **Laparoscopic myolysis** (using laser or coagulation current) and **cryomyolysis** (using a -180°C probe) of leiomyomas have resulted in a persistent decrease in the size of fibroids and appear to be another promising therapeutic option.
 - b. **Hysterectomy** is the definitive treatment for uterine leiomyomas if the indications for surgery are present and **if childbearing is complete and uterine conservation is not important to the individual.**
 - (1) With hysterectomy, both the leiomyomas and any associated disease are removed permanently. There is no risk of recurrence.
 - (2) In patients with abnormal bleeding, other causes should be evaluated and treated before hysterectomy. Hysterectomy should not be performed on the assumption that the bleeding is caused solely by the leiomyomas. Biopsy of the endometrial cavity is essential before hysterectomy to rule out endometrial neoplasia. The absence of cervical malignancy must also be ascertained before surgery.

- (3) The patient's medical and psychological risks should be evaluated before surgical therapy.
 - (4) Ovaries need not be removed when removing the uterus. The patient must play an important part in the decision concerning oophorectomy at any age; little evidence supports the contention that the residual ovary after a hysterectomy is at greater risk for development of ovarian cancer. The long-term consequences of estrogen deprivation—osteoporosis and cardiovascular risk—and implications of estrogen replacement therapy should be addressed thoroughly before surgery. Women with a strong family history of breast or ovarian cancer may benefit from salpingo-oophorectomy and should be counseled appropriately.
- c. **Uterine artery embolization (UAE).** Over the past 15 years, this procedure has emerged as an alternative to traditional surgery. UAE is performed by inserting a catheter into the femoral artery to access the uterine arteries. Small particles, such as gel-foam microspheres or polyvinyl alcohol particles, are injected into the uterine arteries causing occlusion of the blood supply to the uterus and leiomyomas. Thus causing shrinkage or necrosis and death of the leiomyomas. Given its rich collateral blood supply, the uterus will not necrose even if both arteries are occluded.
- (1) Recent studies have shown that UAE is relatively safe. It results in a 60% reduction in size of fibroids and controls menorrhagia in more than 90% of cases.
 - (2) Typical candidates are women with symptomatic fibroids who are approaching menopause, no longer desire fertility, have a large uterus, have multiple health risks for surgery or do not desire surgery, and have uncontrollable menorrhagia.
 - (3) The most common complication seen in UAE is fibroid expulsion, which can be seen in 3% to 5% of patients and occurs most often in patients with submucosal fibroids. Other complications include vaginal discharge, infection, premature ovarian failure, and persistent pain from fibroid necrosis that may rarely necessitate hysterectomy.



Study Questions for Chapter 28

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A 55-year-old woman, gravida 4, para 4, presents to your office for a postoperative visit. You performed an uncomplicated total abdominal hysterectomy and bilateral salpingo-oophorectomy for her history of symptomatic leiomyomas. She has an unremarkable physical examination with a well-healed abdominal scar. You review the pathology report with her, which reveals a normal uterus with multiple leiomyomas and normal tubes and ovaries bilaterally. All of the following are pathologic features of benign leiomyomas **except**:

- ☐ A Pseudocapsule
- ☐ B Smooth muscle fibers intermixed with fibrous connective tissue
- ☐ C Hyaline degeneration
- ☐ D Calcification
- ☐ E Coagulative necrosis

2. A 38-year-old woman, gravida 4, para 4, with a history of myomas, presents to the emergency department reporting pelvic pressure. She denies cardiac, renal, or hepatic symptoms. A pelvic ultrasound shows a 15-cm uterine mass that has the echogenicity of a fibroid. Pressure from this fibroid may also cause:

- ☐ A Leg ulcers
- ☐ B Peau d'orange
- ☐ C Superficial thrombophlebitis of pelvic vessels
- ☐ D Deep venous thrombosis of the leg
- ☐ E Deep venous thrombosis of the pelvic vessels

3. A 48-year-old woman, gravida 4, para 3, spontaneous abortions 1, with known fibroid uterus presents for an annual examination with complaints of heavy vaginal bleeding during her periods and occasional spotting in between periods. She reports that her menses occurs every 29 to 37 days and lasts 7 to 10 days. Her cycle is associated with painful cramps. She is otherwise healthy without chronic medical problems. You note an enlarged, irregular uterus without adnexal masses on her bimanual examination. The next best step in the management of this patient is:

- ☐ A GnRH agonist for 3 months
- ☐ B GnRH agonist for 6 months and add-back hormones for the last 3 months
- ☐ C Hysterectomy
- ☐ D Endometrial biopsy
- ☐ E Transvaginal ultrasound

4. A 46-year-old woman with a known history of uterine fibroids presents with heavy, irregular vaginal bleeding. She reports feeling lightheaded and dizzy, as well as hot flashes and night sweats. Her hemoglobin is 6.4 g/dL and an endometrial biopsy reveals disordered proliferative-phase endometrium. You attempt conservative management without success. You are considering GnRH agonists prior to hysterectomy. The most likely result of this therapy is:

- ☐ A Decrease in hemoglobin
- ☐ B Decrease in uterine size
- ☐ C Decrease in uterine cell number
- ☐ D Degeneration of the fibroids
- ☐ E Improvement in the patient's vasomotor symptoms

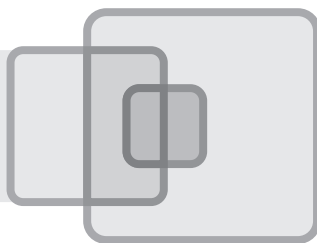
5. A 29-year-old woman, gravida 1, para 0, at 18 weeks of gestation, presents to your office for a routine prenatal visit. She recently had her first obstetrical ultrasound that revealed a normal growing fetus with a posterior placenta and two uterine myomas. She is concerned about the newly diagnosed fibroids and their impact on her pregnancy. All of the following are potential pregnancy-associated complications of fibroids during pregnancy except:

- ☐ A Intrauterine growth restriction (IUGR)
- ☐ B Preterm labor
- ☐ C Breech presentation
- ☐ D Fibroid torsion
- ☐ E Postpartum hemorrhage



Answers and Explanations

1. **The answer is E** [III B 2 b]. Coagulative necrosis and cellular atypia are associated with leiomyosarcomas—a malignant disease of the uterus. The pseudocapsule is a fibrous layer that covers the surface of the fibroid. Leiomyomas are bundles of smooth muscle cells and connective tissue is a whorled pattern. Hyaline degeneration is common to fibroids and calcification can be seen in postmenopausal women.
2. **The answer is E** [IV A 3 e]. Compression of pelvic vasculature by a markedly enlarged uterus can lead to thrombosis of pelvic vessels, which can rarely lead to pulmonary embolus. Deep venous thrombosis of the leg is not associated with leiomyomas. Superficial thrombophlebitis of legs, but not pelvic vessels, may result from stasis of blood in this patient. Peau d'orange is a skin edema that occurs in breast cancer. Leg ulcers are common in patients with a history of advanced diabetes or peripheral vascular disease.
3. **The answer is D** [IV B 2 c]. You cannot assume that abnormal bleeding in a 49-year-old woman is caused by the leiomyomas simply because she has an enlarged uterus. At this age, the risk of endometrial disease, such as polyps, hyperplasia, and carcinoma, is significant and must be evaluated. Thus, endometrial sampling is the most appropriate next step for this patient. Hysterectomy is the definitive treatment for fibroids and is a therapeutic option for someone who is finished with childbearing and who has inadequate relief with medical management such as GnRH agonists. This option can be contemplated in this case only after endometrial carcinoma is ruled out. A transvaginal ultrasound is appropriate in this case but should be considered after performing the endometrial biopsy.
4. **The answer is B** [V B 1]. Reduction in uterine size due to decrease blood flow and cell size is noted in patients taking GnRH agonists. Hemoglobin values should improve with shrinkage in the fibroid size. A decrease in leiomyoma cell number or fibroid degeneration is not observed. GnRH agonists create a hypoestrogenic state and will likely exacerbate the patient's vasomotor symptoms.
5. **The answer is A** [IV A 5]. IUGR is not associated with fibroids however preterm labor is a complication of uterine fibroids. In the third trimester, leiomyomas may be a factor in malpresentation (breech), mechanical obstruction, and uterine dystocia. Torsion of fibroids, particularly pedunculated myomas, may cause acute or gradual pain. Women with fibroids are at risk for postpartum hemorrhage.



The Infertile Couple

ISAAC E. SASSON • STEVEN J. SONDHEIMER

I

INTRODUCTION

- A Infertility** is defined as no conception after 1 year of unprotected intercourse (i.e., without contraception).
1. **Fecundability**, or the monthly probability of pregnancy, is about 20% among fertile couples. The cumulative probability of pregnancy after 1 year approaches 85%.
 2. **Primary infertility** refers to individuals who have never established a pregnancy.
 3. **Secondary infertility** refers to individuals who have conceived previously (including miscarriages) but are currently unable to establish a subsequent pregnancy.
- B Incidence** Approximately 15% of couples are infertile, using the criteria of at least 1 year of unprotected coitus.

II

CAUSES OF INFERTILITY

- A Pathophysiology**
1. Multiple biological processes are required to achieve pregnancy. These include:
 - a. Ovulation
 - b. “Competent oocyte”
 - c. Fallopian tube patency
 - d. Normal uterine cavity and vaginal outflow tract
 - e. Spermatogenesis
 - f. Coitus
 - g. Fertilization
 - h. Embryo implantation
 2. Disruptions of these steps necessary in establishing a pregnancy lead to infertility. The following percentages reflect the prevalence of these factors in infertility evaluations. In 20% to 40% of couples, there are multiple causes of infertility. Therefore, the percentages below add up to more than 100.
 - a. Ovulatory dysfunction: 25%
 - b. Ovarian aging (decreased ovarian reserve): incidence varies with age
 - c. Tubal factor: 35%
 - d. Uterine and vaginal outflow tract abnormalities: 3%
 - e. Endometriosis: 35%
 - f. Male factor: 40%
 - g. Coital problems: 5%
 - h. Unexplained: 10%
- B Ovulatory dysfunction**
1. Definitions
 - a. Inability of the ovaries to release oocytes on a cyclic basis. Normal ovulation requires an **intact hypothalamic–pituitary–ovarian axis**.
 - b. **Anovulation** is lack of ovulation.
 - c. **Oligo-ovulation** is occasional ovulation.

2. Etiology

a. **Androgen excess**

- (1) Polycystic ovarian syndrome
- (2) Nonclassic congenital adrenal hyperplasia
- (3) Androgen-secreting tumors

b. **Hypothalamic amenorrhea**

- (1) Malnutrition
- (2) Weight loss
- (3) Excessive exercise

c. **Hyperprolactinemia**

- (1) Medications (many medication classes, including antipsychotics that are dopamine receptor antagonists; a typical example is haloperidol)
- (2) Pituitary tumors
- (3) Hypothyroidism (Increased thyrotropin-releasing hormone [TRH] secretion stimulates prolactin secretion.)

d. **Decreased ovarian reserve** (see below)e. **Hypothyroidism**

3. Diagnosis

- a. **Predictable, regular menses** (every 28 to 35 days) is a very good predictor of ovulation but does not confirm that ovulation is occurring.
- b. **Basal body temperature monitoring** detects when ovulation has occurred because progesterone, produced by the corpus luteum will cause the basal temperature to rise by 0.5 to 1.0°. The woman takes her temperature upon awakening and before getting out of bed in the morning and graphs the daily temperature. When graphed, a classic **biphasic pattern** is seen with temperatures in the follicular phase on average 0.5° lower than in the luteal phase. This technique is not helpful in predicting when ovulation will occur, but is helpful in determining that ovulation has occurred.
- c. **Urinary luteinizing hormone (LH) kits** may also be used to detect the LH surge that triggers ovulation. Patients begin testing their urine on cycle Day 10 and continue testing until they detect a change in color on the indicator stick. It can be assumed that ovulation will occur within the following 12 to 24 hours.
- d. A **serum progesterone level** greater than 4 ng/mL suggests ovulation. A progesterone level of 10 ng/mL obtained in the midluteal phase (i.e., 7 days from ovulation) represents an adequate level of progesterone and has largely replaced the endometrial biopsy as an assessment of luteal-phase adequacy.
- e. **Luteal-phase endometrial biopsy** is a historic test (first described in 1950) that was done to confirm ovulation and to determine if the endometrium was in an appropriate stage to allow implantation (i.e., “in phase”). However, due to variation in interpretation of the histologic samples and normal variability seen in fertile couples, the test is no longer used.
- f. **Thyroid-stimulating hormone (TSH), prolactin, total testosterone, free testosterone, 17-hydroxyprogesterone, and follicle-stimulating hormone (FSH)** should be assessed if no evidence of ovulation is detected.

4. Treatment

- a. **Correction of underlying endocrine disorders**, such as thyroid disease and hyperprolactinemia, leads to spontaneous ovulation in many patients.
- b. Induction of ovulation
 - (1) **Clomiphene citrate** is the **most commonly prescribed fertility drug and is indicated for the treatment of anovulation**. Clomiphene citrate is an estrogen antagonist and works best in women with a functioning hypothalamic–pituitary–ovarian axis (i.e., women with normal estrogen levels and oligo- or anovulation, such as those with polycystic ovarian syndrome). It triggers endogenous release of FSH, which then stimulates follicular development. Clomiphene citrate is well suited for practitioners and patients because of its oral administration, ease of use, and minimal monitoring. The usual starting dose in anovulatory women is 50 mg daily for 5 days early in the follicular phase (usually cycle Days 5 to 9). Intercourse can be timed by using a urinary LH predictor kit to predict ovulation or by

monitoring follicular development by transvaginal ultrasound. If no measurable response to 50 mg of clomiphene occurs, the dose can be increased by 50 mg in subsequent cycles to a maximum of 150 mg. In **anovulatory women**, each ovulatory cycle induced by clomiphene results in a pregnancy rate of 20%. Cumulatively, the 6-month conception rate in this population is 60% to 75%, mirroring the normal conception rate. The risk of twin pregnancies is 10%, and the risk of higher order multiple pregnancies is less than 1%.

- (2) **Injectable gonadotropins** are indicated primarily for women with hypothalamic amenorrhea or for those who have failed to ovulate with clomiphene treatment. Preparations include purified urinary extract of FSH and LH and laboratory-synthesized FSH preparations. Unlike clomiphene, this drug directly stimulates the ovary. Monitoring involves serial serum estradiol measurements and transvaginal ultrasounds to assess ovarian response. Ovulation will not occur spontaneously and is triggered by injection of human chorionic gonadotropin (hCG; similar structure to LH hormone, which is the natural trigger for ovulation) after both estradiol levels and follicular size suggest follicular maturity. In hypothalamic amenorrheic women, the 6-month conception rate approaches 90%. This rate is lower in women with other causes of anovulation. The risk of twin pregnancies is 10% to 20%, and the risk of higher order multiple pregnancies is less than 5% but is dependent on the number of mature follicles developed.

C Diminished ovarian reserve

1. A woman's chronologic age and the aging of the ovary correlate with the number and quality of available oocytes and are two independent predictors of fertility.
 - a. **Age of the woman** is an important predictor of fertility.
 - (1) Age-related infertility rates in three age groups are as follows:
 - (a) 25 to 29 years: 9%
 - (b) 30 to 34 years: 15%
 - (c) 35 to 39 years: 22%
 - (2) Spontaneous loss rates are higher in older women because of higher risk of aneuploidy
 - b. **Ovarian aging concept.** It is generally accepted that there is a finite number of oocytes in a 46,XX individual. The maximum oocyte number is actually achieved in utero. Throughout a woman's lifetime there is a steady and uninterrupted depletion of oocytes independent of ovulation. Ovarian aging is termed "decreased ovarian reserve" and correlates with a decrease in fertility.
2. Diagnosis through **markers of decreased ovarian reserve**
 - a. Elevated menstrual **cycle Day 3 FSH** is a marker of decreased oocyte number and quality.
 - (1) **FSH** level on the third day of the menstrual cycle that is greater than 10 to 12 mIU/mL is considered elevated and correlates with a decrease in fertility. A range is given because these "threshold" levels can vary in value and interpretation in different laboratories. This FSH level is still considered in the "normal" premenopausal range.
 - (2) An elevated **estradiol** level (greater than 80 pg/mL) on the third day can also represent a decrease in ovarian reserve, but it is not as predictive as the FSH level. An elevated estradiol level may suppress the FSH level through negative inhibition and falsely portray a "normal" FSH level.
 - b. An **antral follicle count** is performed by using transvaginal ultrasound to visualize the ovaries and to count the total number of follicles measuring 2 to 5 mm. A low antral follicle count predicts diminished response to fertility treatment.
 - c. The **clomiphene citrate challenge test** is a **bioassay to FSH response** that reflects ovarian follicular capability. Following administration of clomiphene citrate 100 mg/d on cycle Days 5 to 9, an FSH level on menstrual cycle Day 10 is compared with a baseline FSH level on menstrual cycle Day 3. An FSH value on either Day 3 or Day 10 that is greater than or equal to the threshold level for the laboratory is associated with a decreased likelihood of achieving pregnancy.
 - d. Anti-müllerian hormone (AMH) is a substance produced by granulosa cells in ovarian follicles. A level of less than equal to 1.0 ng/mL correlates with decreased number of oocytes and poor prognosis for fertility. This test is relatively new, and more information is needed before it can be used exclusively to determine ovarian reserve of prognosis.

3. **Treatment.** Fertility treatment for a patient with decreased ovarian reserve should be approached more aggressively. The chance of success with any treatment option is lower than in an individual with normal ovarian reserve and the patient should be counseled appropriately. The decision to proceed should be individualized and must take into account likely success, which depends on the age of the woman and any other factors identified that could affect fertility.
 - a. **Donor oocytes** through in vitro fertilization can be fertilized with partner sperm, and the embryo(s) can be transferred to and carried by the woman.
 - b. **Donor embryo** is a relatively new option for couples. Excess embryos from prior in vitro fertilization (IVF) cycles are donated by the biologic parents to other couples and transferred into the woman's uterus of the recipient couple.
 - c. Adoption.

D Tubal factor

1. **Tubal disease.** The fallopian tube is responsible for efficient **transfer of gametes** and transport of the dividing embryo to the uterine cavity. It provides an environment in which capacitation of spermatozoa, fertilization, and early development of the embryo take place. Tubal disease or blockage can impair the ability to conceive. Common causes of tubal disease include **pelvic inflammatory disease, tubal ligation, and endometriosis**.
2. Diagnosis
 - a. **Hysterosalpingography (HSG)** is a fluoroscopic study that provides visualization of the **uterine cavity and internal lumen and patency** of the fallopian tube using a radiopaque dye injected through the cervix. This method neither allows for visualization of the external surface of the tubes nor provides external assessment of pelvic adhesions or anatomic relationships within the pelvis. A hysterosalpingogram is usually obtained before performing a laparoscopy because it is less costly and less invasive.
 - b. **Laparoscopy** allows direct visualization of the external surface of the fallopian tube to identify abnormalities in structure or location and to detect peritubal or pelvic adhesions. Laparoscopy does not provide any information on tubal patency unless a dye (usually indigo carmine) is injected through the cervix and is allowed to spill into the pelvic cavity under direct visualization.
3. Treatment
 - a. **IVF** bypasses the fallopian tube and is the most successful and avoids surgery. However, conception can only be attempted when doing IVF
 - b. Surgical allows monthly natural exposure for couples but an increased risk for ectopic pregnancy.
 - (1) **Tubal reanastomosis** for sterilization reversal
 - (2) Lysis of peritubal adhesions
 - (3) Neosalpingostomy and fimbrioplasty for treating hydrosalpinges. Involves opening the distal end of fallopian tube at laparoscopy or laparotomy. Associated with a 10% to 25% chance of ectopic pregnancy and tube reclosure rate depending on the degree of tubal damage
 - (4) Bilateral salpingectomy to remove hydrosalpinges prior to IVF instead of opening the tubes surgically. Hydrosalpinges are associated with a 50% decrease in live birth rate with IVF, so it is recommended to remove the occluded tubes prior to doing IVF.

E Uterine abnormalities

1. **Uterine factor.** The uterus is responsible for providing an environment suitable for sperm transport, development of the embryo prior to implantation, and carriage of the pregnancy. The following abnormalities are associated more with pregnancy loss than infertility.
 - a. **Leiomyomas** (fibroids): especially submucosal in location
 - b. **Uterine polyps**
 - c. **Synechiae:** scar tissue from prior uterine procedures, also known as Asherman syndrome
 - d. **Congenital anomalies** such as uterine septum or bicornuate or unicornuate uterus. Also included in this is vaginal/uterine agenesis
 - e. **Cervical factor:** cervical procedures, such as cone biopsy or loop electrosurgical excision procedures (LEEPs) for cervical dysplasia may remove a significant portion of the cervix and adversely affect production of cervical mucus. This can potentially affect fertility by reducing sperm transport to the uterus

2. Diagnosis

- a. **HSG** allows visualization of the internal contour of the uterine cavity by injection of a radiopaque dye under fluoroscopic radiography through the cervix. Aside from detecting tubal pathology, this **technique detects synechiae, congenital anatomic anomalies, and polyps and fibroids** if they distort the uterine cavity. Abnormalities detected on HSG should be further characterized with either a sonohysterogram or hysteroscopy.
- b. **Sonohysterogram** utilizes a small volume of saline to distend the uterine cavity while transvaginal ultrasonography is performed. The distension displaces the opposing uterine walls and permits better characterization of intracavitary filling defects. Indirect information about tubal patency can be inferred by presence of fluid in the cul de sac following the procedure which suggests at least one fallopian tube is patent.
- c. **Hysteroscopy** allows for direct visualization of the uterine cavity to confirm the abnormality and allows simultaneous surgical treatment of the abnormality noted. Although the tubal ostia are visualized with hysteroscopy, no information is obtained about tubal patency with this technique.
- d. If a congenital uterine anomaly is suspected after HSG, a pelvic **magnetic resonance image (MRI)** may be helpful to noninvasively assess the external and internal contours of the uterus. This technique also allows inspection of the urinary tract given a high rate of associated anomalies. Laparoscopy is a more invasive method of obtaining information about the external contour of the uterus.

3. Treatment

- a. **Surgical correction.** Many abnormalities, including synechiae, fibroids, polyps, and uterine septae, can be surgically corrected at the time of hysteroscopy.
- b. **IVF** can be performed in patients without an intact uterus, and embryos can be transferred to and carried in a **gestational carrier**.

F Endometriosis

- 1. **Endometriosis** (see Chapter 27) is a common gynecologic disorder estimated to affect 71% of women with pelvic pain alone and nearly 85% of women with both infertility and pelvic pain. Endometriosis is postulated to affect fertility through:

- a. **Anatomic distortion** of the ovaries, fallopian tubes, and uterine position secondary to endometriotic lesions or adhesions
- b. Other *hypothesized* mechanisms, including:
 - (1) Interference in oocyte pick-up by the fimbriae and inhibition of fertilization due to increased concentration of macrophages, prostaglandins, interleukin-1, and tumor necrosis factor in the peritoneal fluid of patients with endometriosis
 - (2) Altered endometrial receptivity
- c. Although the exact mechanism for endometriosis affecting fertility has not been elucidated, its role is suggested by the following:
 - (1) Laparoscopic correction of minimal or mild endometriosis results in a small but significant improvement in fertility.
 - (2) IVF outcomes are worse in patients with moderate and severe endometriosis.

2. Diagnosis

- a. **Laparoscopy with visual confirmation of endometriotic lesions or biopsy-confirmed histology** is the only way to confirm the diagnosis.
- b. History of worsening or severe dysmenorrhea and/or pre- or postmenstrual bleeding is suggestive, but not diagnostic, of endometriosis.
- c. A **pelvic ultrasound**, especially if done by the vaginal route, can often diagnose echogenic ovarian masses that correspond to **endometriomas** (“chocolate cysts”). The presence of endometriomas suggests the possibility of moderate to severe endometriosis.

3. Treatment

- a. **Surgical ablation and adhesiolysis** typically by laparoscopy is the treatment of choice in those with moderate to severe disease. Surgical treatment of minimal or mild disease results in a small but significant (8%) increase in pregnancy rates.

- b. **Empiric fertility treatment** without laparoscopic confirmation of endometriosis can be undertaken, especially if mild or minimal endometriosis is suspected.
- c. **Gonadotropin-releasing hormone (GnRH)** agonist therapy is not indicated for treatment of endometriosis in those who are trying to conceive.

G Male factor infertility

1. Male factor infertility occurs when abnormalities in semen volume, sperm count, motility, or morphology significantly affect a couple's ability to conceive. **Paternal age** greater than 40 years is associated with a 20% greater chance of birth defects in the offspring; although the absolute risk remains very low.
2. Initial evaluation
 - a. **Semen analysis** should be the initial test obtained on all males in couples seeking evaluation. The sample is generally collected by masturbation after 2 to 3 days of abstinence. Ideally two samples obtained at least 6 weeks apart should be analyzed. The World Health Organization standards are as follows:
 - (1) **Volume:** 1.5 to 5.0 mL
 - (2) **Concentration:** greater than 20 million sperm/mL
 - (3) **Total sperm number:** greater than 40 million per ejaculate
 - (4) **Percent motility:** greater than 50%
 - (5) **Progression:** greater than 2 (scale 0 to 4)
 - (6) **Morphology:** more than 30% with normal, oval heads, and a single tail
 - (7) **White blood cells:** less than 1 million/mL
 - b. Differential diagnosis
 - (1) **Oligospermia** is an ejaculate with less than 20 million sperm per milliliter. **Severe oligospermia** is present when an ejaculate contains less than 5 million sperm per milliliter.
 - (2) **Azoospermia** is complete absence of sperm in the ejaculate.
 - (a) Obstructive azoospermia occurs when production of sperm is normal, but there is an obstruction that prevents sperm being ejaculated: vasectomy, congenital bilateral absence of vas deferens (CBAVD), postsurgical obstruction.
 - (b) Nonobstructive azoospermia occurs when production of sperm is severely affected—hypogonadotropic hypogonadism: Kallmann syndrome, pituitary tumors; testicular failure: chemotherapy/radiation, trauma, mumps, idiopathic; chromosome abnormalities: Klinefelter syndrome (47,XXY), translocations/deletions, Y chromosome microdeletions.
 - (3) **Teratospermia** is reduced sperm morphology.
 - (4) **Asthenospermia** is reduced sperm motility.
3. Evaluation of the male with azoospermia or severe oligospermia (in absence of prior vasectomy or vasectomy reversal)
 - a. Review of medications, medical history, surgical history (especially inguinal hernia operations as a child, testicular injury or surgery)
 - b. **FSH and testosterone levels** to evaluate for hypo- or hypergonadotropic disorders
 - c. **Karyotype:** 10% to 15% of azoospermic men will have an abnormal karyotype. Klinefelter syndrome is the most common and accounts for two-thirds of chromosomal abnormalities in infertile men
 - d. **Y chromosome microdeletion** is found in 10% to 15% of men with azoospermia or severe oligospermia. These deletions are not seen on a karyotype. This test is performed by polymerase chain reaction (PCR), followed by gel electrophoresis
 - e. Prolactin and TSH if indicated
 - f. Testicular ultrasound
 - g. **Cystic fibrosis screening** in congenital bilateral absence of the vas deferens (CBAVD). Approximately two-thirds of men with CBAVD will have a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene
 - h. Referral to a urologist for examination

4. Treatment. In deciding how to proceed with the treatment of the male, the factors identified in the female must be considered.
 - a. Medical therapies include:
 - (1) Correction of underlying hormonal disorders (e.g., thyroid disorders, prolactin excess, and dietary disturbances)
 - (2) Use of hCG to stimulate sperm production in cases of hypothalamic dysfunction
 - b. **Surgical therapies** can be performed for varicocele and vasectomy reversal; however, neither repair should be performed when IVF is indicated for the female partner.
 - (1) Varicocele repair can be considered in men who have all of the following criteria: a palpable varicocele; known infertility; normal female fertility; and abnormal semen parameters. Whereas, semen parameters may improve after repair, the impact of the surgery on achieving pregnancy remains unclear.
 - (2) Vasectomy reversal may not be advised if the female partner is older due to the length of time needed for sperm to be seen in the ejaculate after reversal.
 - c. **Intrauterine insemination** with sperm. This technique involves washing the semen specimen to concentrate the actively motile sperm and placing the specimen high in the reproductive tract, closer to the fallopian tubes, at the time of ovulation. This technique is performed in conjunction with administering a fertility drug to the female. This procedure is well suited to mild male factor infertility as well as unexplained infertility.
 - d. **IVF**. This technique is indicated as primary treatment in those with severe oligospermia or in cases of obstructive and nonobstructive azoospermia with surgical collection of sperm. It is combined with intracytoplasmic sperm injection (ICSI) to achieve fertilization. Surgical techniques to acquire sperm for IVF/ICSI include:
 - (1) Percutaneous epididymal sperm aspiration
 - (2) Testicular sperm aspiration/extraction (biopsy)
 - (3) Microsurgical testicular sperm extraction
 - e. Insemination with **donor sperm** can be performed in a woman's natural ovulatory cycle or in combination with fertility drugs or IVF.

H Coital problems

1. The **most fertile days** are up to 6 days prior to ovulation and on the day of ovulation. Coitus should occur during this period.
2. Diagnosis by **history**. It is important to establish that vaginal penetration and ejaculation are occurring and that successful intercourse is occurring during the most fertile days. In some ethnic groups, ideal timing of coitus is difficult due to a mandatory waiting period between the end of menses and when intercourse is allowed.
3. **Regular coitus** starting 4 to 5 days prior to ovulation and continuing beyond when ovulation has occurred, at least every other day, without long intervals of abstinence, is the best way to ensure that the fertile window is included.

I Unexplained infertility

1. Unexplained infertility refers to couples in whom **no identifiable causes or mild abnormalities** are present, such as mild male factor or minimal to mild endometriosis. It affects 10% to 20% of couples with infertility.
2. Diagnosis. Diagnosis of exclusion: A laparoscopy is not necessary to make the diagnosis.
3. Treatment. **Empiric superovulation with either clomiphene citrate or injectable gonadotropins, along with timed intrauterine insemination (IUI), is usually attempted before considering assisted reproductive technology.** During superovulation the follicular growth and number is monitored by ultrasound and serum estradiol levels; hCG injection is used to induce ovulation, and timed IUI of washed concentrated sperm, resuspended in a balanced salt solution free of semen proteins and prostaglandins, is also used. Unlike with ovulatory infertility, where unifollicular development is desired, development of three to five follicles is the goal. The problem with this treatment, however, is the risk of high-order multiple gestation because there is no control over how many oocytes fertilize or implant.

III

EVALUATION OF THE INFERTILE COUPLE

- A** A full infertility evaluation is not usually initiated until 1 year of coitus without contraception. Premature evaluation has the risk of initiating treatment when pregnancy might have occurred spontaneously in a relatively short time.
- B Evaluation should begin sooner in:**
 1. Women older than 35 years of age and those with irregular or absent menses
 2. History of pelvic inflammatory disease or sexually transmitted diseases
 3. History of pelvic surgery, ruptured appendix in the female
 4. Significant history in the male partner
- C Initial evaluation includes:**
 1. A thorough medical and surgical history of both the male and female partners
 2. Cycle Day #3 FSH/estradiol
 3. Cycle Day #3 ultrasound to assess antral follicle count and uterine and ovarian anatomy
 4. Semen analysis
 5. Hysterosalpingogram to evaluate the uterine cavity and patency of the fallopian tubes
 6. Endocrine evaluation including TSH and prolactin
 7. Confirmation of ovulation by luteal phase progesterone level
- D** Additional testing can be tailored to risk factors identified in the couple's history.
 1. **Laparoscopy** may be indicated in women with abnormalities detected on the initial evaluation above, or in those with a history of PID or pelvic surgery where adhesions are suspected or in cases of severe dysmenorrhea to evaluate and treat endometriosis, especially if IVF (which would bypass intrapelvic disease) is not an option for the couple.

IV

TREATMENT OF THE INFERTILE COUPLE

- A Approach to treatment** Once the decision to begin evaluation has been made, goals of treatment are as follows:
 1. Seek out and correct causes of infertility
 2. Provide accurate information and dispel misinformation
 3. Provide emotional support, including listening, giving plenty of time for questions, and lending support without blame or criticism
 4. Provide **preconception counseling**
 - a. Smoking cessation and minimal alcohol exposure
 - b. Folic acid supplementation to decrease the risk of neural tube defects in the fetus
 - c. Genetic counseling
 - d. Advanced maternal age carries a higher risk of chromosomal abnormalities and advanced paternal age carries high risk for new autosomal dominant conditions in the fetus
 - e. Indicated carrier states: certain ethnic populations have a higher risk of genetic problems in the offspring
 - (1) Ashkenazi Jewish individuals: Tay–Sachs disease, cystic fibrosis, Canavan disease, Bloom syndrome, Familial dysautonomia, Fanconi anemia, Gaucher disease, Niemann–Pick disease
 - (2) African Americans: sickle cell disease
 - (3) Mediterranean individuals: thalassemia
 - (4) Caucasians: cystic fibrosis
 - f. A family history of genetic abnormalities in the couple or first-degree relatives, such as congenital cardiac anomalies and mental retardation, could potentially be passed to the fetus.
 5. Maternal–fetal medicine consultation for medical illnesses that could affect the health of the mother or fetus during pregnancy such as diabetes and chronic hypertension

6. Provide options for treatment and alternatives when treatment has not been successful or is not possible. Referral to a counselor can be very helpful in dealing with the stress of infertility.

B Treatment approach

1. Target treatment towards the causes identified during the evaluation for infertility.
2. Decide if a diagnostic laparoscopy is advised to evaluate for other pelvic factors missed by initial testing. This decision may depend on feasibility for the couple to do IVF. In states where IVF coverage is mandated, fewer laparoscopies are done to evaluate and treat potential pelvic factors causing infertility.
3. The standard therapy for couples with infertility (assuming open fallopian tubes and presence of sperm) includes superovulation with IUI and IVF.

C **Superovulation with IUI** This involves using fertility drugs to produce multiple follicles and therefore multiple oocytes and using IUI to place the sperm high up in the uterine cavity and closer to the fallopian tubes at the time of ovulation. This technique aims to facilitate oocyte and sperm interaction, thereby improving the chances of conception per cycle. Options for fertility drugs are as follows:

1. **Clomiphene citrate** is a selective estrogen receptor modulator (SERM) which binds the estrogen receptor in the pituitary, so the body perceives a low level of estrogen which stimulates endogenous secretion of FSH and stimulates follicular development. Dosing is 50 to 150 mg daily for 5 days (CD 4 to 8) of the cycle, but the lowest effective dose should be used. IUI is timed by ovulation predictor kit or hCG injection. With clomiphene citrate the average number of follicles/oocytes per cycle is 1 to 2, rarely more. Therefore, the risk of multiple gestation with clomiphene citrate is 10% chance of twins and less than 1% triplet pregnancy rate. Success rates for unexplained infertility depend on maternal age and sperm status but on average are 10% per cycle.
2. **Aromatase inhibitors** such as letrozole have also been used. These medications are administered orally for 5 days just like clomiphene citrate. The multiple gestation rate is slightly lower than with clomiphene citrate.
3. **Gonadotropins:** Preparations include purified urinary extract of FSH and LH and laboratory-synthesized FSH preparations. Unlike clomiphene these drugs directly stimulate the ovary to produce multiple follicles, the goal is 2 to 4. These medications are administered by injection (usually subcutaneous) and monitoring involves serial serum estradiol measurements and transvaginal ultrasounds to assess ovarian response. Ovulation will not occur spontaneously and is triggered by injection of hCG after both estradiol levels and follicular size suggest follicular maturity. IUI is timed by hCG injection. Multiple gestation risk correlates with number of follicles achieved and rates are 20% to 40%. For couples with unexplained infertility +/- mild male factor, cumulative pregnancy rates for up to four cycles of gonadotropin with IUI are approximately 30%.
4. **Assisted reproductive technology** is indicated for the initial treatment of severe male factor and obstructed fallopian tubes. However, indications also include all other causes of infertility where other treatments have failed to achieve a pregnancy. IVF is the most successful treatment available, but it is also the most aggressive treatment and therefore decision to proceed is based on the relative risks and benefits for the individual couple.
 - a. **IVF** involves ovarian follicular stimulation followed by **ultrasound-guided oocyte retrieval**. The oocytes are then fertilized with sperm in the laboratory, and resultant embryos are transferred back into the uterus.
 - (1) **Injectable gonadotropins** are used to stimulate ovaries to produce multiple follicles.
 - (2) Endogenous ovulation/LH surge is suppressed through **pituitary suppression** with GnRH agonists and antagonists.
 - (3) Ovulation is triggered by hCG because it is more stable than LH and has an almost identical structure (hCG shares the α -subunit as LH, and β -subunit differs by only 30 amino acids).
 - (4) Approximately 36 hours after exogenous stimulation of ovulation, oocytes are usually retrieved transvaginally under ultrasound guidance. In rare circumstances, oocytes can be retrieved transabdominally, transvesically, and laparoscopically.

- (5) Oocytes are incubated with sperm in a dish to allow for fertilization overnight. Fertilized eggs are then monitored for division.
 - (6) **Embryo transfers** back into the uterus through the cervix typically occur on **Day 3** (8- to 10-cell stage) or **Day 5** (blastocyst stage) after retrieval.
 - (7) **The number of embryos transferred depends on age, embryo morphology, and prior patient history.** In the United States, there are guidelines from the American Society of Reproductive Medicine to help direct the number of embryos transferred. In multiple European countries, there are guidelines for single embryo transfers. The goal is to ensure successful pregnancies and deliveries while minimizing the number of multiple pregnancies.
 - (8) **Success rates** depend on the age of the woman. Data from IVF programs in the United States registered with the Society for Assisted Reproductive Technology (SART) for all causes of infertility in 2008 show that for a woman who is less than 35 years of age, live birth rate following IVF and transfer of embryos into the uterus was 47.1%. In a woman greater than 42 years of age, live birth rates per embryo transfer was 6.8%.
- b. **ICSI** is a micromanipulation technique whereby a single sperm is injected directly into the cytoplasm of the oocyte to enhance fertilization. This method is often used for **male factor infertility**. Pregnancy rates are independent of any semen analysis parameter because sperm are directly injected into ova by an embryologist.
 - c. In **preimplantation genetic diagnosis (PGD)**, a single cell or polar body is biopsied from the embryo prior to embryo transfer during an IVF cycle and subjected to genetic testing. Currently, this technique is most often used in identifying affected embryos of single gene disorders such as Gaucher disease and cystic fibrosis. With the results from testing, an unaffected embryo is transferred back into the uterus. PGD serves as an alternative to chorionic villus sampling or amniocentesis for diagnosis and possible abortion of affected fetuses.
 - d. **Ovarian hyperstimulation syndrome (OHSS)** is a complication of IVF. It is a self-limiting disorder that results from an exaggerated ovarian response to gonadotropin stimulation. Vascular endothelial growth factor (VEGF) secretion from the ovary results in increased systemic vascular permeability resulting in fluid shifts from the vasculature into the third space. HCG has been shown to induce VEGF expression. As a result patients who develop OHSS from their stimulation and then become pregnant have a greater risk of prolonged and more severe course.
 - (1) **Risk factors** include young age, low BMI, PCOS, high doses of gonadotropin, estradiol levels greater than 5,000 pg/mL and prior OHSS.
 - (2) **Clinical features** range across a spectrum that include abdominal discomfort and distension, nausea and vomiting, to rapid weight gain, tense ascites, hemodynamic instability, tachypnea, oliguria. Severe disease can result in decreased renal perfusion, pulmonary compromise, and thromboembolism as a result of hemoconcentration. In extreme cases patients may suffer from acute respiratory distress syndrome (ARDS) or ovarian rupture.
 - (3) **Management** is determined by the severity of the disease. Mild and moderate symptoms can be managed as an outpatient supportively with fluid restriction and monitoring of weight and urine output. Serious illness may require hospitalization for fluid management, pain control, close monitoring, or therapeutic interventions. Patients with symptomatic ascites or tachypnea may be treated with paracentesis. Electrolyte abnormalities should be corrected. Hemodynamically unstable patients can be treated with an albumin infusion to expand the vascular volume. Hemoconcentrated patients with a hematocrit greater than 45% should be treated with prophylactic anticoagulation.
 - (4) **Prevention** is critical to avoiding OHSS complications. Ovulation induction regimens should be individualized to provide the minimum dose and duration of gonadotropin treatment. Careful identification of at-risk patients should be made prior to stimulation. Patients with high estradiol levels may have gonadotropin withheld or their cycle cancelled to prevent OHSS. The final stage of oocyte maturation may be performed with lower doses of hCG or a GnRH agonist.

5. **Decreased ovarian reserve (DOR).** Fertility treatment for a patient with decreased ovarian reserve should be approached more aggressively. The chance of success with any treatment option is lower than in an individual with normal ovarian reserve. The decision to proceed should be individualized and must take into account likely success, which depends on the age of the woman and any other factors identified that could affect fertility.
- a. **Donor oocytes** through in vitro fertilization can be fertilized with partner sperm, and the embryo(s) can be transferred to and carried by the woman
 - b. Donor embryo
 - c. Adoption



Study Questions for Chapter 29

Directions: Match each clinical scenario with the most likely cause of infertility. Each answer may be used once, more than once, or not at all.

QUESTIONS 1–6

- ☐ A Ovulation
- ☐ B Oocyte equality
- ☐ C Tubal factor
- ☐ D Uterine factor
- ☐ E Male factor
- ☐ F Unexplained

1. A 25-year-old woman, gravida 2, para 2, has been attempting pregnancy for the past 2 years. She has no medical problems. She had surgery for a ruptured appendix 5 years ago. Her periods are regular and last 3 to 4 days. She denies smoking, drinking alcohol, or using drugs. Her husband is 28 years old, is healthy, and has a normal sperm count.
2. A 29-year-old woman, gravida 5, para 1, with a history of four terminations of pregnancy by suction curettage, presents to you because she has not been able to conceive since her last termination 3 years prior. Since that time she notes that her periods although regular have become much lighter and lasting only 2 days. Her husband is 34 years old and is healthy.
3. A 30-year-old nulligravid woman presents to you because she and her husband have been trying to get pregnant for the past 2 years. She has no prior medical history. She has regular, 30-day menstrual cycles and denies dysmenorrhea. Her pelvic examination is normal. Laboratory testing on cycle Day 3 is normal. Ovulation is confirmed by a midluteal-phase progesterone level. You perform a hysterosalpingogram that shows a normal uterine cavity and patent bilateral fallopian tubes. Her husband is 31 years old and has a normal semen analysis.
4. A 42-year-old woman, gravida 1, para 0 (spontaneous abortion 4 years ago), presents with 2 years of secondary infertility. She has no other medical history and has regular 30-day menstrual cycles. On her pelvic ultrasound, you noted an antral follicle count of four from the two ovaries. The hysterosalpingogram that you performed showed a normal uterine cavity and bilateral tubal patency. Her husband's semen analysis is normal.
5. A 27-year-old woman, gravida 2, para 2, with regular cycles, presents to you because she has not been able to get pregnant after reversal of her husband's vasectomy. She has no medical problems.
6. A 22-year-old nulligravid woman and her husband have been trying to get pregnant for the last 18 months. She has no known medical problems and has never had any surgery. She says her periods are irregular. She gets about four to five periods per year. She is 5 feet 2 inches tall and weighs 210 lb. On review of systems, she reports hair growth on her abdomen and chin.

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

7. A 28-year-old nulligravida presents to your office with a 1-year history of infertility. She has regular cycles, a normal HSG and hormonal evaluation. A transvaginal ultrasound is unremarkable with a normal antral follicle count. Her partner has never conceived a child. He has a normal semen analysis but

a urologist reports that he has palpated a prominent varicocele. A laparoscopy 2 years prior noted mild endometriosis. The next best step in helping this couple achieve pregnancy is:

- ☐ A Review timed intercourse and continue expectant management
- ☐ B 3 months of GnRH agonist therapy
- ☐ C Conventional IVF and embryo transfer
- ☐ D Superovulation with clomiphene citrate and IUI
- ☐ E Varicocele repair followed by timed intercourse

8. A 26-year-old nulligravid and her 26-year-old husband are seeing you because they have not been able to get pregnant for the last 3 years. The woman has regular periods every 30 days that last 4 days. Both of them have no medical problems or past surgical history. Both deny smoking, caffeine use, herbal remedy use, alcohol abuse, or drug use. The husband's sperm analysis reveals a volume of 2.5 mL, total count less than 0.1×10^6 sperm/mL, 10% normal motility, and 30% normal morphology. The next best step in management of this couple is:

- ☐ A Superovulation with clomiphene citrate and IUI
- ☐ B IVF with ICSI and embryo transfer
- ☐ C Conventional IVF and embryo transfer
- ☐ D Karyotype, FSH, testosterone, Y microdeletion testing
- ☐ E Superovulation with injectable gonadatropins and IUI

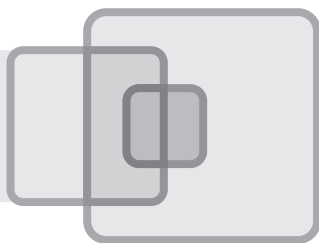


Answers and Explanations

1. **C [II D]**, 2. **D [II E]**, 3. **F [II I]**, 4. **B [II C]**, 5. **E [IV C 6]**, 6. **A [II B 2]**. In Question 1, the woman has had surgery for a ruptured appendix. When an intra-abdominal infection is present (from either a ruptured viscus or pelvic inflammatory disease), there is a risk of adhesion formation, including adhesion of the fallopian tubes to other structures. This prevents proper egg retrieval and transport by the tube, which can lead to ectopic pregnancy. This diagnosis can be confirmed by hysterosalpingogram or laparoscopy. In Question 2, this patient most likely has Asherman's syndrome. Vigorous uterine curettage can disrupt the basalis layer of the endometrium, which may preclude the normal endometrial proliferation that occurs during the secretory phase of the cycle. The first step would be a pelvic ultrasound followed by a hysterosalpingogram or hysteroscopy. During surgery a uterine lysis of adhesions can be performed in an attempt to restore the normal uterine cavity. Postoperatively this patient should be managed with an intrauterine balloon and hormone therapy to prevent reformation of the uterine adhesions. In Question 3, the couple has a normal infertility workup, rendering the diagnosis of exclusion: unexplained infertility. A laparoscopy is not necessary to make this diagnosis. In Question 4, this older patient has a low antral follicle count and an otherwise normal workup. Her infertility is likely due to decreased ovarian reserve. A cycle Day 3 FSH and estradiol level would be helpful in confirming the diagnosis. In Question 5, reversal of vasectomy may not work. A semen analysis would show azoospermia. The next step would be to use donor sperm versus percutaneous epididymal sperm aspiration performed in conjunction with IVF. In Question 6, this patient's signs and symptoms suggest polycystic ovarian syndrome. These patients are oligo-ovulatory.

7. **The answer is D [II F 1/ IV C 5]**. The exact mechanisms through which mild endometriosis affects fertility have not been elucidated. Women with mild endometriosis have decreased fecundity. Superovulation with IUI is predicted to overcome this defect by increasing the number of oocytes available for fertilization. IUI increases the number of sperm present in the fallopian tube. Taken together, this approach increases the number of gametes in the reproductive tract in any given month. GnRH agonist therapy is not indicated for treatment of endometriosis in those who are trying to conceive. This couple has been attempting expectant management for the past year and remains unsuccessful. Intervention is warranted at this time. IVF would be the most effective means to achieving pregnancy but more conservative and less costly interventions should be attempted first. Varicocele repair is not recommended for the male partner since he has a normal semen analysis and the impact of the surgery on achieving pregnancy remains unclear.

8. **The answer is D [II G 3]**. In this clinical scenario, it appears that the wife is ovulatory and has no reason for having tubal or uterine abnormalities. The husband, however, has abnormal sperm parameters, namely severe oligospermia. The workup of severe oligospermia includes a karyotype to evaluate for Klinefelter syndrome and Y chromosome microdeletion testing. These abnormalities have implications not only for this couple's fertility, but also for possible transmission to their offspring and therefore should be performed prior to treatment. ICSI is a micromanipulation technique in which sperm is injected directly into the cytoplasm of the oocyte to enhance fertilization. This method is often used for severe male factor infertility (as in this case). Should this couple proceed with fertility treatment after workup of severe oligospermia, they will most likely undergo IVF with ICSI. In cases of severe male factor, IVF with ICSI has better success than conventional IVF (without ICSI). Sperm washing with IUI combined with fertility drug treatment in the woman is a treatment for mild oligospermia, but in this situation, the sperm count is so low that IUI is not likely to be successful.



Ectopic Pregnancy

KURT BARNHART • LAUREN W. MILMAN

I

INTRODUCTION

An ectopic pregnancy is implantation of an embryo outside the uterus.

A Location

1. **Tubal (99%):** anywhere in the fallopian tube
 - a. The most common site is the ampulla.
 - b. Interstitial (cornual) pregnancies occur in the most proximal tubal segment, which runs through the uterine cornua. This type of ectopic pregnancy can grow to be quite large, and rupture may cause massive hemorrhage.
2. **Ovarian (0.5%):** on the ovary
3. **Abdominal (less than 0.1%):** in the abdomen, with possible adherence to the peritoneum, visceral surfaces, or omentum
4. **Cervical (0.1%):** in the cervix
5. **Heterotopic**
 - a. Both intrauterine and ectopic pregnancies may occur concomitantly.
 - b. This type of ectopic pregnancy is extremely rare (1 in 4,000 in the general population and 1 in 100 in those who conceived with in vitro fertilization [IVF]).
6. **Cesarean section scar.** Risk of ectopic pregnancy at a prior cesarean section scar site is very rare, but potentially life-threatening because of the thin layer of uterine wall and scar tissue to which the pregnancy has implanted. There is increased risk of this type of pregnancy with shortened interval between prior uterine surgery and subsequent pregnancy.

B Prevalence Ectopic pregnancies constitute 2% of all pregnancies. This proportion has increased over the past few decades, but true prevalence is not known.

C Significance Ectopic pregnancy may lead to tubal rupture, massive intra-abdominal hemorrhage, and, ultimately, death. It also may result in tubal damage and has been associated with a poor reproductive outcome. It is the leading pregnancy-related cause of death in the first trimester. With reliable serum pregnancy tests and vaginal ultrasound, early detection and treatment of an ectopic pregnancy is possible.

II

ETIOLOGY

A General considerations The occurrence of ectopic pregnancy has been associated with abnormal function of the fallopian tubes. Normally, the tubes facilitate collection and transport of the oocyte and embryo into the uterus. The integrity of the fimbria, lumen, and ciliated mucosa appears to be important for transport. Conditions thought to prevent or retard migration of the fertilized ovum to the uterus increase the risk for an ectopic pregnancy. However, up to half of all women who are diagnosed with an ectopic pregnancy do not have any risk factors.

B Pelvic inflammatory disease (PID) The inflammation and scarring of intra- and extraluminal structures resulting from PID impair normal tubal function and foster implantation in the tube. Severe damage may lead to complete tubal blockage and infertility.

- C Tubal surgery** Bilateral tubal ligation and tubal reanastomosis may lead to scarring and narrowing of the tube or false passage formation. There is a 1% to 3% failure rate for bilateral tubal ligation, and as many as one-third of patients who have a subsequent pregnancy will have an ectopic pregnancy. Pelvic and abdominal surgeries may also result in peritubal adhesions but have not been directly associated with ectopic pregnancy.
- D Infertility and assisted reproductive techniques** Infertility is a risk factor for developing an ectopic pregnancy, presumably due to undetected tubal disease, though other factors may be present. Studies have documented increased risk of ectopic pregnancy with treatments for infertility including IVF, gamete intrafallopian transfer, and superovulation, regardless of previous tubal damage. Retrograde embryo migration may be a possible mechanism.
- E Cigarette smoking** Studies have shown that cigarette smoking causes tubal ciliary dysfunction. Smoking has been associated with ectopic pregnancy.
- F Intrauterine device (IUD)** Like any contraceptive method, the IUD protects against ectopic pregnancy. However, women who become pregnant with an IUD in place have a higher chance of having a tubal pregnancy than women without an IUD.

III

SIGNS AND SYMPTOMS

- A Vaginal bleeding** Light vaginal bleeding or spotting in the first trimester of pregnancy is the most common symptom of ectopic pregnancy. This bleeding usually begins 7 to 14 days after the missed menstrual period, and patients may interpret the bleeding as a menses.
- B Abdominal pain** Unilateral pelvic pain is the second most common symptom. The pain may become severe and diffuse and may be associated with shoulder pain (caused by diaphragmatic irritation from intra-abdominal blood) if significant intra-abdominal hemorrhage exists.
- C Other symptoms** Dizziness, fainting spells, and palpitations from hypotension resulting from intra-abdominal hemorrhage may occur.
- D Pregnancy status** The standard urine pregnancy test is usually positive in the presence of an ectopic pregnancy. However, an ectopic pregnancy may be associated with a lower than expected human chorionic gonadotropin (hCG) level for gestation, and may not be detected in the urine test. The serum pregnancy test, which is more sensitive, should be performed if the urine test is negative and clinical suspicion is high.

IV

DIAGNOSIS

Because the symptoms of vaginal bleeding and pain in early pregnancy are not specific for ectopic pregnancy, these findings should not be used in isolation to diagnose this condition.

- A Differential diagnosis**
 1. Spontaneous or threatened abortion
 2. Adnexal torsion
 3. Appendicitis
 4. PID
 5. Hemorrhagic corpus luteum
 6. Endometriosis
 7. Diverticulitis
 8. Ovarian cyst
- B Physical examination** In the presence of tubal rupture with intra-abdominal hemorrhage, patients may be hypotensive and tachycardic. In these cases, abdominal distention from hemoperitoneum and signs of an acute abdomen may be present with guarding, rebound, and cervical

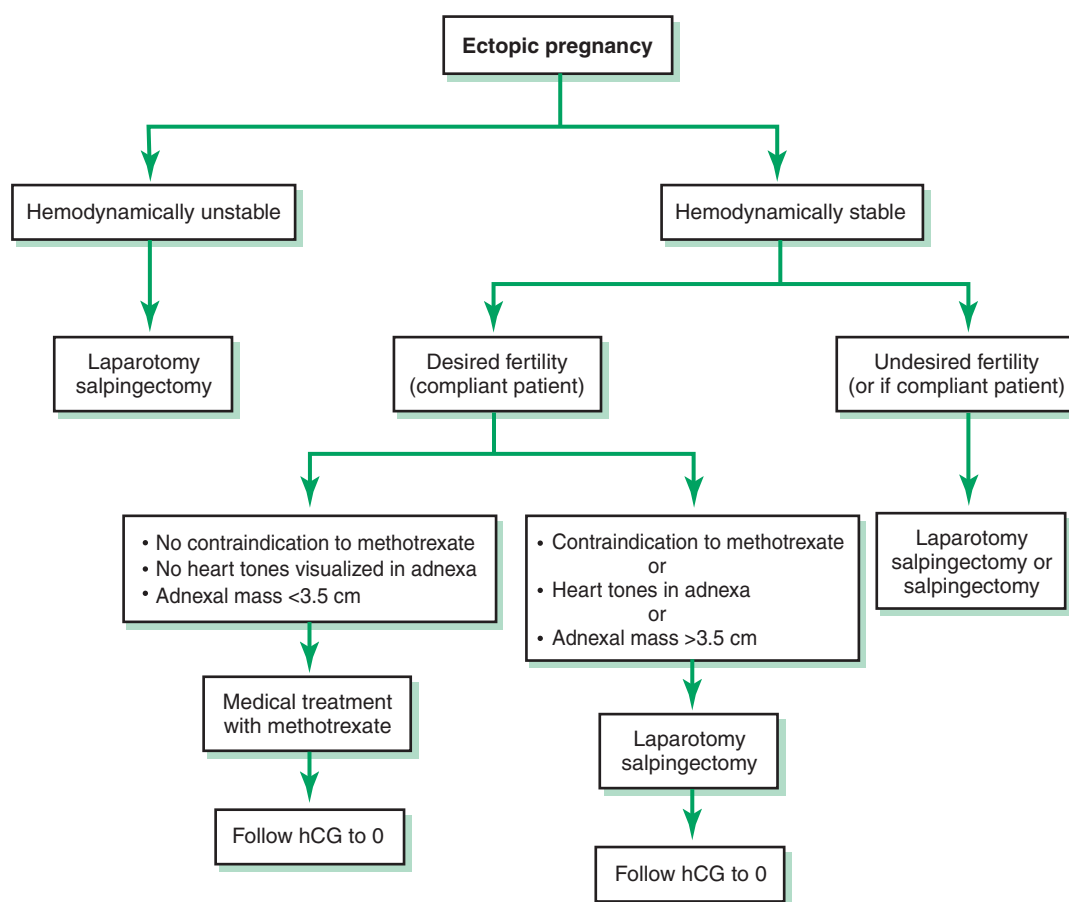


FIGURE 30–1 Treatment algorithm for ectopic pregnancy. hCG, human chorionic gonadotropin.

motion tenderness. In the absence of rupture, the physical examination may be completely normal. An unruptured ectopic pregnancy cannot be diagnosed by physical examination alone.

C Diagnostic tests No single diagnostic test detects all ectopic pregnancies. A diagnostic strategy has been devised involving the use of several diagnostic modalities (Fig. 30–1).

1. Transvaginal ultrasound. The first step in the evaluation of a suspected ectopic pregnancy is transvaginal ultrasound.

- It is difficult to diagnose an ectopic pregnancy by ultrasound alone. However, all viable intrauterine pregnancies can be visualized by transvaginal ultrasound at a gestational age greater than 5.5 to 6 weeks. Therefore, the **best way to diagnose** an ectopic pregnancy is to **rule out the presence of an intrauterine pregnancy** (heterotopic pregnancies are extremely rare).
- If an intrauterine pregnancy is detected on ultrasound, then ectopic pregnancy has essentially been excluded. If an ectopic pregnancy is visualized, then treatment may be pursued. If the ultrasound is nondiagnostic, then further evaluation is required.

2. Human chorionic gonadotropin

- This hormone, which is produced by trophoblastic tissue, increases linearly in early pregnancy. hCG is used as a surrogate marker for gestational age because the exact gestational age at the time of presentation is often unknown and serial values can assess the viability of a pregnancy.
- The **discriminatory zone** is defined as the quantitative hCG level above which all intrauterine pregnancies are visible by ultrasound. It is not the lowest hCG at which an intrauterine pregnancy can be visualized. The hCG level for transvaginal ultrasound, which varies by institution, is approximately 2,000 mIU/mL. A higher discriminatory zone will decrease the possibility of interrupting a viable gestation.

- c. If an intrauterine pregnancy is not identified by transvaginal ultrasound when the quantitative hCG level is higher than the discriminatory zone, then the gestation is, by definition, nonviable (either an abnormal intrauterine pregnancy or an ectopic pregnancy).
3. **Dilation and curettage (D&C).** When an intrauterine pregnancy is not identified by transvaginal ultrasound and the hCG level is greater than the discriminatory zone, a D&C may be performed to determine the location of the gestation. The absence of chorionic villi in the curettage specimen suggests the presence of an extrauterine, or ectopic, pregnancy.
4. **Serial hCG testing**
 - a. If the quantitative hCG is below the discriminatory zone and the ultrasound is nondiagnostic, it is necessary to follow serial quantitative hCG levels to distinguish a viable intrauterine pregnancy from a nonviable gestation. Early in viable pregnancies, the **hCG concentration increases in a reproducible fashion** (minimum increase, 50%). If the hCG level increases above the discriminatory zone, a repeat ultrasound should be performed to confirm the presence of an intrauterine pregnancy.
 - b. **hCG levels that fall or stabilize indicate nonviable pregnancies.**
 - (1) When hCG levels decrease, they should be followed until the concentration of hCG is undetectable to confirm the diagnosis of a complete abortion. hCG levels should fall 21% to 35% in 2 days for a woman with a spontaneous abortion (depending on the initial value). Ruptured ectopic pregnancies have occurred at very low hCG concentrations.
 - (2) When hCG levels fail to rise or decline “normally,” a D&C should be performed to distinguish a nonviable intrauterine pregnancy from an ectopic pregnancy.
5. **Laparoscopy.** If the diagnosis is in doubt, laparoscopy may be performed to directly visualize the tubes and ovaries.
6. **Serum progesterone levels.** These measurements may be used as an adjunct to ultrasound and hCG. Progesterone levels less than 5 ng/mL are usually associated with nonviable pregnancies, and levels of 25 ng/mL or higher are usually associated with viable intrauterine pregnancies. However, these values are not absolute. Most patients evaluated for ectopic pregnancy have intermediate values, which are not helpful in diagnosis. The usefulness of progesterone is controversial.

V

TREATMENT

- A Surgical approaches** Surgical treatment of ectopic pregnancy has the advantage of taking care of the ectopic immediately.
1. **Salpingectomy**, the removal of the fallopian tube containing the ectopic pregnancy, is the treatment of choice in the following situations:
 - a. Future childbearing is not desired.
 - b. The tube is severely damaged.
 - c. Bleeding cannot be controlled.
 - d. The ectopic is in a fallopian tube where an ectopic occurred previously.
 - e. The ectopic is in a fallopian tube that had previously been operated on. In the case of prior tubal ligation, bilateral salpingectomy should be performed to decrease the risk of future ectopic in either tube.
 2. **Linear salpingotomy**, the removal of the gestation through a linear incision in the fallopian tube, may be performed if future fertility is desired.
 - a. This procedure is associated with a persistent ectopic pregnancy rate of 3% to 20%.
 - b. Therefore, serial quantitative hCG values must be followed to ensure resolution.
 3. **Operative laparoscopy** may be performed to confirm the diagnosis of ectopic pregnancy and to remove the abnormal gestation via salpingectomy or salpingostomy. This method is typically used in hemodynamically stable patients. Advantages of this technique over laparotomy include:
 - a. Shorter hospital stay
 - b. Faster postoperative recovery
 - c. Better cosmetic result
 - d. Potentially shorter operative time

4. **Laparotomy** is typically reserved for hemodynamically unstable patients who require emergent surgery for a ruptured ectopic pregnancy. This method may also be appropriate when laparoscopy is contraindicated or technically challenging because of extensive adhesive disease from prior surgery.
5. **Cornual resection** may be performed when an interstitial pregnancy occurs. The interstitial portion of the tube is removed via wedge resection into the uterine cornu. Cornual ectopic pregnancies have a higher failure rate with methotrexate and a surgical approach may be more effective.
6. **Oophorectomy** is indicated only when an ovarian ectopic pregnancy occurs and salvage of the affected ovary is not possible.

B Medical approach Methotrexate (MTX), a chemotherapeutic agent, has been used successfully to treat some patients who have an ectopic pregnancy. This approach has the advantage of avoiding surgery, but the patient must be counseled that it may take 3 to 4 weeks for the ectopic to resolve with methotrexate therapy.

1. **Mechanism of action.** Methotrexate is a folic acid antagonist that interferes with DNA synthesis. Its action is principally directed at rapidly dividing cells, such as trophoblastic cells, but it affects all rapidly dividing cells, including the bone marrow, gastrointestinal mucosa, and respiratory epithelium. Methotrexate is toxic to hepatocytes and is cleared by the kidneys.
2. **Clinical considerations and contraindications.** Patients can be considered candidates for methotrexate use if they are willing to comply with follow-up and laboratory surveillance, do not have pain attributed to the ectopic pregnancy, do not have signs of hemodynamic instability or rupture of the ectopic pregnancy, have a gestational sac that is less than 3.5 cm, and do not have evidence of fetal cardiac activity. Absolute contraindications include women who are breastfeeding or who have immunodeficiency, liver disease, renal disease, blood disorders, peptic ulcer disease, and active pulmonary disease. Methotrexate should not be used if there is any possibility of a viable gestation as it is both an abortifacient and a teratogen.
3. **Administration.** Methotrexate may be administered in a single intramuscular dose, two intramuscular injections 3 days apart, or in multiple dose regimen with folic acid “rescue” (Table 30–1). Use of multiple doses of MTX reduces the failure rate. Serial hCG levels are followed every 2 to 4 days until the hCG level starts to decrease. Once the hCG level is falling, then hCG levels can be checked weekly.
4. **Success rates** for methotrexate in treating ectopic pregnancy have been shown to be 73% to 94%. Decreased success has been noted with ectopic pregnancies of greater than 3.5 cm, with fetal cardiac activity, or with high hCG levels. Tubal patency rates following methotrexate treatment are 70% to 80%, making this a reasonable option for those wishing to preserve their fertility.
5. **Treatment success** using *single-dose methotrexate* is decreased if the initial hCG value is greater than 5,000.

TABLE 30–1 Methotrexate Treatment in Ectopic Pregnancy

Treatment Regimen	Single Dose	Two Dose	Multidose
Methotrexate	50 mg/m ² Day 1	50 mg/m ² Days 1 and 4	1 mg/kg Day 1 (may be 3, 5, and 7)
Leucovorin	None	None	0.1 mg/kg alternating with methotrexate
hCG monitoring	Days 1, 4, and 7	Days 1, 4, and 7	Every other day, then weekly until hCG has decreased by 15%
Repeat dose	Day 7 if hCG did not decline 15% during Days 4 through 7	Day 7 if hCG did not decline 15% during Days 4 through 7	Administer until hCG declines 15% or up to four doses
Surveillance hCG values	Weekly until level is undetectable	Weekly until level is undetectable	Weekly until level is undetectable

hCG, human chorionic gonadotropin.

6. **Treatment failures.** Surgical management is usually necessary.
7. **Follow-up.** Serial hCG measurements must be observed after treatment until no longer detectable to ensure resolution of the pregnancy.
8. **Complications** (approximately 5% of patients). Mild gastrointestinal symptoms such as nausea, vomiting, diarrhea, and stomatitis are typical. Potential life-threatening complications are rare and can include pneumonitis, thrombocytopenia, neutropenia, elevated liver function tests, and renal failure.

VI**PROGNOSIS**

- A Fertility** Tubal patency after conservative surgical therapy (salpingotomy) or methotrexate is similar: approximately 70% to 80%. As many as 80% of women achieve pregnancy after an ectopic pregnancy, but only 33% deliver live infants. The best chance for future pregnancy in cases of tubal occlusion is in vitro fertilization.
- B Recurrence** Of those women who achieve pregnancy after an ectopic pregnancy, as many as 27% will have another ectopic pregnancy. All patients should be told about the recurrence risk and should notify a physician as soon as a menses has been missed to determine the location of the pregnancy.



Study Questions for Chapter 30

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A 28-year-old woman, G2, P0, S1, is in the emergency room complaining of spotting for the past week. Her last normal menstrual period was approximately 5 weeks ago. You have obtained a serum b-hCG, which was 1,220 IU/L, and a transvaginal ultrasound was performed, which revealed no gestational sac in the endometrial cavity, no adnexal masses, and no free fluid in the cul-de-sac. The next best step in the management of this patient is:

- ☐ A Repeat b-hCG in 2 days
- ☐ B Laparoscopy
- ☐ C Laparotomy
- ☐ D Methotrexate, single-dose therapy
- ☐ E Dilation and curettage

2. A 28-year-old woman, gravida 2, para 1, ectopic 1, presents to your clinic for an annual examination. She and her partner would like to try to have another child. Her menstrual cycles are regular, occurring every 28 days. You tell her that it is very important for her to give you a call or to come back to the clinic if she misses her period. The reason for this advice is:

- ☐ A Given her history, she has a 33% chance of delivering a live infant
- ☐ B She needs a urine pregnancy test to rule out another ectopic
- ☐ C Her risk of a recurrent ectopic is approximately 15%
- ☐ D Her risk of a recurrent ectopic is approximately 25%
- ☐ E She is at increased risk for PID

3. A 23-year-old woman, gravida 3, para 1, ectopic 1, presents to your office because she missed her last period and has felt a sharp, intermittent pain in her left lower abdomen. She has no past medical history other than a left-sided ectopic pregnancy a few years ago successfully treated with methotrexate, several years after vaginal delivery of her only son. Her serum β -hCG level is 10,500. On physical examination, her BP = 110/74, P = 90, and T = 97.8. She is obese and lacks peritoneal signs, and no masses are appreciated. A transvaginal ultrasound performed in your office reveals no gestational sac in the uterus and a 4.3-cm mass in the left adnexa separate from the ovary. What is the next best step in management of this patient?

- ☐ A Laparoscopic salpingostomy
- ☐ B Laparoscopic salpingectomy
- ☐ C Methotrexate
- ☐ D Exploratory laparotomy
- ☐ E Repeat β -hCG in 2 days

4. A 36-year-old nulligravid woman is seeing you for her annual gynecologic care. She has a past medical history significant for pulmonary fibrosis. Within the past 3 years, all of the following are remarkable in her chart: bacterial vaginosis, *Candida*, chronic endometritis, pyelonephritis, history of IUD that was removed 5 years ago, and history of infertility for which she was treated with fertility drugs and IVF. She is a nonsmoker but does admit to drinking two to three alcoholic beverages every day. She has a family history significant for colon cancer in her maternal aunt. Which of the following places her at greatest risk for an ectopic pregnancy?

- ☐ A Age
- ☐ B Pulmonary fibrosis
- ☐ C Past IUD use
- ☐ D Infertility
- ☐ E Chronic endometritis

5. A 24-year-old woman, gravida 3, para 1, spontaneous abortions 1, presents to the emergency room reporting irregular vaginal bleeding. She is found to be pregnant and her serum hCG is 3,500 mIU/mL. She has a past medical history significant for diabetes mellitus and mild asthma. Her BP = 103/68, P = 88, and T = 98.8. Transvaginal ultrasound reveals a uterus with no gestational sac present and a 2-cm right adnexal mass. The best treatment of choice is:

- ☐ A Expectant management
- ☐ B Methotrexate
- ☐ C Laparoscopic salpingostomy
- ☐ D Laparoscopic salpingectomy
- ☐ E Laparotomy

6. A 37-year-old female presents to the emergency department complaining of mild lower pelvic pain that started earlier today. Her last menstrual period was 6 or 7 weeks ago. She had a tubal ligation 5 years ago and admits that she does not keep track of her menstrual cycles since then. On evaluation she is found to have a serum hCG of 2,553, with ultrasound showing a thin endometrial lining without evidence of pregnancy and a 2-cm mass in the right adnexa but no free fluid. You recommend the following treatment:

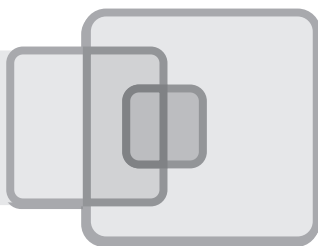
- ☐ A Methotrexate therapy with 2 dose regimen
- ☐ B Methotrexate therapy with single dose regimen
- ☐ C Laparoscopy with right salpingectomy
- ☐ D Laparoscopy with bilateral salpingectomy
- ☐ E Folic acid replacement



Answers and Explanations

1. **The answer is A** [IV C]. When the quantitative hCG level is below the discriminatory zone (usually 2,000 mIU/mL, depending on the ultrasound machine) and no pregnancy is visualized by transvaginal ultrasound, no conclusive diagnosis can be made, and the patient should return in 2 days for repeat hCG level, and if it is then above the discriminatory zone, repeat ultrasound can be performed to aid in diagnosis of intrauterine or ectopic pregnancy. Determining the location of the pregnancy is important not only to establish the correct treatment, but also to counsel the patient regarding her risk of having an ectopic in a subsequent pregnancy. Methotrexate would not be ideal at this point because it is not clear that the patient has an ectopic pregnancy since there is no pregnancy identified in the uterus and there is no sign of a pregnancy in the tubes by ultrasound. If diagnosis of an ectopic pregnancy has been confirmed by finding no chorionic villi at D&C, then methotrexate would be an option. Neither a laparoscopy nor a laparotomy is necessary yet because no mass has been visualized on ultrasound.
2. **The answer is D** [VI B]. Of those women who achieve pregnancy after an ectopic pregnancy, as many as 27% will have another ectopic pregnancy. All patients should be counseled about the risk of recurrence. A urine pregnancy test is not as sensitive as a serum hCG and should not be used as the definitive test to determine if a patient is pregnant. Also, a pregnancy test alone cannot differentiate between ectopic and intrauterine pregnancy. This patient is not at increased risk for PID based on the information provided. Although the patient with a history of a prior ectopic does have a 33% chance of delivering a live infant, this would not be the reason to bring her back to the office if she misses a period.
3. **The answer is B** [V A]. This patient most likely has an ectopic pregnancy in the left fallopian tube, the same tube where she had a prior ectopic pregnancy. The best treatment option is to remove the tube since her rate of another ectopic in the same tube is high. She presumably has another fallopian tube and therefore future pregnancy is possible. Salpingotomy would not be a good idea because leaving the tube in would place the patient at a very high risk for recurrence of another ectopic pregnancy. Methotrexate is contraindicated because the hCG level is too high and the size of the ectopic is too big (greater than 3 cm). In addition, treating with methotrexate would place the woman at high risk for another left-sided ectopic. Repeating hCG in 2 days is inappropriate because you already know that the hCG level is above the discriminatory level, there is no intrauterine gestation, and there is a mass in the left adnexa, so you have a diagnosis of ectopic pregnancy. Repeating the hCG level would give you no additional information and would just delay the treatment, risking rupture of the ectopic. In a patient who is hemodynamically stable, a laparotomy is not necessary, unless there are medical indications to avoid laparoscopy or the patient has known or suspected intra-abdominal adhesions that would make laparoscopy difficult.
4. **The answer is D** [II D]. Infertility is a risk factor for ectopic pregnancy. Current IUD use, not past IUD use, places the patient at risk for ectopic pregnancy. Chronic endometritis is not associated with ectopic pregnancy because this inflammation does not involve the fallopian tubes. Age is not a risk factor for ectopic pregnancy. Pulmonary fibrosis is not a risk factor for ectopic pregnancy but would be a contraindication for methotrexate.
5. **The answer is B** [V B]. This patient has an ectopic pregnancy that is amenable to treatment with methotrexate because she has no contraindications (hCG not high, less than 3-cm adnexal mass, and mild asthma and diabetes mellitus are not contraindications). Although methotrexate and linear salpingostomy have comparable rates of tubal patency and fertility, methotrexate is the least invasive. Expectant management of a growing ectopic pregnancy is not appropriate given possibility of rupture and hemorrhage, which can be catastrophic. Salpingectomy is not preferred to salpingostomy in someone who desires future fertility. Laparotomy is not indicated in this patient, who is hemodynamically stable.

6. **The answer is D** [V A 1]. This patient has an ectopic pregnancy as she has an hCG level above the discriminatory level and no identifiable gestation in the uterus. The best treatment option is to perform a laparoscopy with bilateral salpingectomy. The rationale is that she already decided on sterilization and does not want to have any more children. She is an example of the low failure rate of tubal ligation. To avoid future pregnancy or future ectopic pregnancies, bilateral salpingectomy is the treatment of choice. Removal of the affected tube is an option, but still leaves her at risk for another ectopic from the left side. Re-cauterizing (or re-ligating) the left tube would be an option for this patient, but is not one of the choices. Methotrexate would treat the ectopic well, but would still leave her at risk for subsequent pregnancy and ectopic pregnancy. Folic acid is advised in pregnancy, but patients taking methotrexate should be counseled to avoid folic acid (vitamin supplements) or foods that contain folic acid (most breakfast cereals are fortified) as folic acid interferes with the effectiveness of methotrexate.



Recurrent Pregnancy Loss

DIANA CHAVKIN • SAMANTHA BUTTS

Recurrent pregnancy loss (RPL) is one of the most devastating conditions for couples wishing to conceive. The grief experienced by a couple affected with this disorder is often compounded by frustration due to the fact that many will have an evaluation that reveals no identifiable cause of their pregnancy losses. Couples affected with RPL require specialized care and genuine empathy focusing on complete evaluation, adequate explanation, and sound guidance in their pursuit of subsequent pregnancies.

I

DEFINITION

- A** RPL is defined as the occurrence of three or more *consecutive spontaneous abortions (SAB)* of clinically recognized pregnancies prior to 20 weeks of gestation (excluding molar, biochemical, and ectopic pregnancies). Some authorities consider two consecutive miscarriages sufficient to warrant an evaluation for RPL, especially if there is a history of infertility or advanced maternal age.
1. SAB, pregnancy loss, and miscarriage are interchangeable terms.
 2. If a miscarriage occurs after ultrasound identification of a viable pregnancy with a demonstrable fetal heartbeat (approximately 7 weeks' gestational age), the miscarriage may be characterized in one of two ways:
 - a. Early spontaneous miscarriage: before 12 weeks' gestation
 - b. Late spontaneous miscarriage: after 12 weeks' gestation
 3. These designations are important because certain causes of RPL are more or less common depending on the gestational age of the pregnancy at the time of the loss. For instance, genetic causes are less common after 10 weeks' gestation.
 4. Recurrent fetal loss at or beyond 14 weeks of gestation is infrequent.

II

INCIDENCE

- A** The overall risk of miscarriage is 30% to 50% of all conceptions. This number includes very early losses that may not be clinically apparent but were detected by measuring human chorionic gonadotropin (hCG) levels after the expected window of implantation but prior to a missed menses.
- B** The risk of miscarriage in the first trimester at a gestation of greater than or equal to 6 weeks is approximately 15%. After one miscarriage, the risk of another is not increased (i.e., still 15%). However, the risk does increase after two consecutive miscarriages to 17% to 31%, and after three miscarriages the risk increases to 25% to 46%. **Therefore, healthy women should not have an extensive evaluation for causes of pregnancy loss after one first-trimester miscarriage.**
- C** RPL affects 3% to 5% of couples who are trying to establish a family.
- D** The risk of RPL increases with maternal age, and this trend parallels the general increase in odds of miscarriage in older women.

III

ETIOLOGY OF MISCARRIAGES IN THE GENERAL REPRODUCTIVE POPULATION

- A** **Advanced age** There is an increased risk of chromosomal nondisjunction in oocytes from older women predisposing to inappropriate chromosome number (aneuploidy) in the embryos derived from these oocytes.

1. Risk of clinical pregnancy loss in women younger than 35 years of age: 9% to 12%
 2. Risk of clinical pregnancy loss in women older than 40 years of age: up to 45%
- B Chromosome anomalies** account for 50% of miscarriages and the risk increases with maternal age. The majority of these are due to aneuploidy.
- C Fetal congenital anomalies** are associated with a higher rate of miscarriage, but they may not be associated with gross chromosome anomalies.
- D Structural anomalies of the uterus**
1. Uterine fibroids especially those in submucosal location
 2. Müllerian anomalies mostly associated with second-trimester losses.
- E Endocrine conditions.** Highest risk when these conditions are poorly controlled.
1. Hypothyroidism
 2. Diabetes

IV

ETIOLOGY AND EVALUATION OF RPL

- A** The etiology of RPL is unknown in 50% or more of cases, and couples have a completely normal evaluation. Evaluation should include:
1. History including details of prior pregnancies, circumstances including gestation of each loss, relevant family and genetic history, medical and surgical history.
 2. Physical examination including an evaluation for endocrinopathies and pelvic examination.
- B Anatomic causes** account for 15% of RPL. The prevalence of congenital uterine anomalies is 10% to 15% in women with RPL compared to 7% in general population.
1. **Müllerian anomalies** have been strongly associated with early RPL and second-trimester loss. These anomalies arise from failure of the embryologic precursors of the reproductive tract to develop normally (see Chapter 21).
 - a. During normal female embryologic development, paired müllerian ducts arise, which are destined to develop into the fallopian tubes and fuse to form the uterus, cervix, and upper third of the vagina.
 - b. Müllerian anomalies can arise if this process does not occur properly. Pregnancy failure in the setting of müllerian anomalies is thought to be the result of poor uterine vascularization and/or limited uterine volume.
 - (1) **Uterine septum** results when fusion of the paired müllerian ducts has occurred normally but the medial septum between the ducts has not been completely resorbed. This is the most common uterine abnormality diagnosed in women with RPL.
 - (2) **Unicornuate uterus** occurs when one of the paired müllerian ducts fails to develop; a hemi-uterus with a limited cavity size results.
 - (3) **Bicornuate uterus** arises due to the incomplete fusion of the müllerian ducts resulting in two separate uterine cavities joined at a common cervix.
 - (4) **Uterine didelphys** is the result of complete failure of the müllerian ducts to fuse, but normal differentiation of each duct system. The final outcome is two separate hemi-uteri and cervices, with each uterine horn smaller than a normal uterus.
 2. **Other structural abnormalities in the uterus**
 - a. Uterine fibroids are benign, fibromuscular tumors that arise in the uterus. Fibroids in a submucosal location are believed to cause miscarriages because of inadequate blood supply if the placenta implants on the fibroid. Tumors greater than 5 cm are usually implicated.
 - b. Constricted uterine cavity may limit early fetal growth and development.
 - (1) **Asherman syndrome** are adhesions within the endometrial cavity that result from instrumentation of the cavity usually in the presence of infection following dilation and curettage.
 - (2) **Prior myomectomy** can result in a distortion of the uterine cavity.
 - (3) **Diethylstilbestrol** drug exposure in utero was associated with a small “T-shaped” uterus. This drug was taken off the market in 1971.

3. Diagnosis of uterine abnormalities. Several imaging modalities exist to evaluate the uterus for abnormalities during the workup for RPL. Each modality has benefits and drawbacks. Selection of a particular imaging modality depends on accessibility, pretest suspicion, and patient characteristics.

- a. **Hysterosalpingogram (HSG).** Radiographs of the pelvis are performed while radio-opaque dye is instilled into the uterine cavity. This is usually the first-line test for patients suspected of having uterine anomalies as a cause for RPL.
- b. **Ultrasound.** Real-time images of the pelvis are acquired using sound waves. This modality is excellent for diagnosing size and location of fibroids, but less accurate for diagnosing uterine septum.
- c. **Saline sonohysterography.** Saline is instilled into the uterine cavity while ultrasound is performed. This test highlights the shape of the uterine cavity.
- d. **Magnetic resonance imaging (MRI).** Multiplanar images of the pelvis are generated with the use of magnets rather than X-rays. MRI is superior to HSG for distinguishing a bicornuate uterus from a uterine septum.
- e. **Hysteroscopy.** This minor surgical procedure involves direct visualization of the uterine cavity with a camera attached to hysteroscope. This is the gold standard for evaluating the cavity for müllerian anomalies and can also be used for correcting uterine septums and removing submucosal fibroids, polyps, and adhesions.

C Genetic/parental chromosomal abnormality An occult chromosomal abnormality in either the male or female partner is the cause of RPL in 3% to 5% of all cases. These chromosomal abnormalities are termed “occult” because the individuals who carry them have a normal amount of DNA and appear normal (normal phenotype). However, portions of their chromosomes are rearranged in a way that makes them less capable of producing cytogenetically normal gametes and predisposes to RPL. These chromosome abnormalities are detected by obtaining a karyotype on the male and female partners.

1. **Aneuploidy.** Segregation of homologous chromosomes during meiosis in gametes of the affected parent often results in duplication or deficiency of chromosome segments. If an unbalanced gamete from the carrier of the translocation joins with a balanced gamete from the partner, embryonic aneuploidy (abnormal chromosome number) and early pregnancy loss can ensue.
2. **Parental balanced translocations are most common.** A chromosomal translocation involves the exchange of genetic material between nonhomologous chromosomes. When the translocation is “balanced,” no genetic material is lost and the affected individual will typically be asymptomatic. This occurs, for instance, when the distal portion of one chromosomal arm is exchanged for the distal portion of a second chromosome. Two new chromosomes emerge from this exchange.
3. **Reciprocal translocation accounts for 60% of translocations seen with RPL.** This occurs when the distal portion of one chromosomal arm (e.g., A* from parent chromosome A) is exchanged for the distal portion of a second chromosome (e.g., B* from parent chromosome B) during meiosis.
 - a. Two new chromosomes emerge from this exchange.
 - (1) A with a distal portion of B (B*).
 - (2) B with a distal portion of A (A*).
 - b. As no DNA is lost during this translocation, the affected individual is “balanced” and shows no outward evidence of the rearrangement.
 - c. In many cases, adults with balanced translocations are initially diagnosed during an evaluation for RPL.
4. **Robertsonian translocation** occurs when genetic information is exchanged between two acrocentric chromosomes. **Acrocentric chromosomes** are unique because their centromeres are near the end of the chromosome and their short arms encode redundant genes (chromosomes 13, 14, 15, 21, and 22).
 - a. During a robertsonian translocation, the long arms of two acrocentric chromosomes fuse at the centromere and the two short arms are completely lost.
 - b. A person carrying a robertsonian translocation appears completely normal because the loss of nonessential, redundant DNA on the short arms of the involved chromosomes is well tolerated.
 - c. As is the case with those who have reciprocal translocations, gametes of the affected individual may become unbalanced.

5. **Chromosomal inversions** involve the rearrangement of a segment of the chromosome such that it is reversed within itself. DNA is rarely lost and the affected individual appears normal. While some inversions have been associated with production of unbalanced gametes and RPL, in general, they account for a very small percentage of abnormal parental chromosomes in RPL.

D Antiphospholipid syndrome (APS) accounts for approximately 15% of RPL. It is an autoimmune condition characterized by poor obstetric outcomes (recurrent or late pregnancy loss, stillbirth) and thrombophilia in the setting of autoantibodies that cause hypercoagulation and thrombosis in vivo.

1. With APS, autoantibodies promote placental thrombosis and inflammation and may impair normal invasion of fetal trophoblastic tissue into maternal blood vessels/uterine endometrium. The end result is increased risk of pregnancy loss.
2. According to recent recommendations (2006 criteria from the 11th International Congress) the diagnosis of APS can only be made when one clinical and once laboratory criteria are fulfilled. There can be no more than 5 years separating the clinical manifestation of APS and the laboratory diagnosis.
 - a. **Clinical criteria (one of two)**
 - (1) **Thrombosis:** At least one episode of venous or arterial vascular thrombosis, which should be confirmed by radiologic imaging, such as Doppler studies
 - (2) **Pregnancy morbidity (one of three):**
 - (a) At least one unexplained fetal death(s) of a morphologically normal fetus that is at least 10 weeks' gestation
 - (b) At least one premature birth of a morphologically normal neonate less than or equal to 34 weeks' gestation, due to either eclampsia/preeclampsia or placental insufficiency as evidenced by fetal testing suggestive of fetal hypoxia, oligohydramnios, or postnatal birth weight less than the 10th percentile for gestational age
 - (c) Three or more *consecutive* SAB before the 10th week of gestation, with other causes excluded
 - b. **Laboratory criteria (at least one of the following)**
 - (1) **Anticardiolipin antibodies (ACL)**, IgM or IgG, in medium or high titers (while these are rarely standardized across laboratories, they are commonly reported as greater than 40 GPL [IgG] or MPL [IgM] units, or greater than the 99th percentile of anticardiolipin antibodies within a normal population). The antibodies are measured directly. The same antibody must be elevated on at least two occasions, at least 12 weeks apart.
 - (2) **Lupus anticoagulant antibodies (LAC)**. In contrast to ACL, lupus anticoagulants are not measured directly. Functional in vitro assays of clotting times are used to test for the presence of LAC. These assays are based on the *paradoxical* finding that while the presence of LAC causes increased thrombosis clinically, LAC prolongs tests of clotting time when measured in the laboratory (in vitro). In order for this test to be positive, the following assays must be positive on two occasions and at least 12 weeks apart.
 - (a) Prolonged phospholipid-dependent coagulation on a screening test, such as activated partial thromboplastin time (aPTT), kaolin clotting time, dilute Russell viper venom time, dilute prothrombin time, or Textarin time
 - (b) Failure to correct the prolonged clotting time by mixing with normal platelet-poor plasma
 - (c) Shortening or correcting of the prolonged coagulation time by the addition of excess phospholipids
 - (d) Exclusion of other coagulopathies
 - (e) It is important to emphasize that although the **APS** causes abnormal clotting clinically, lupus anticoagulants cause prolonged bleeding in vitro
 - (3) **Anti β 2 glycoprotein-1 antibodies** should also be measured. In order to meet the criteria for APS diagnosis, they should be elevated (IgG and/or IgM greater than 99th percentile of anti β 2 glycoprotein-1 antibodies within a normal population) on two or more occasions at least 12 weeks apart.

E Thrombophilias other than APS can predispose to microvascular thrombosis which then impairs placental development and growth leading to SAB. Usually this affects second- and third-trimester fetal loss with intrauterine growth restriction, placental abruption, and pre-eclampsia. A relationship with early pregnancy loss has not been clearly established.

1. Implicated inherited coagulopathies include: factor V Leiden, prothrombin gene mutation, Protein S deficiency, Protein C deficiency, and antithrombin as well as other thrombophilic factors such as VIII and XIII.
2. Thrombophilia work-up is **only** indicated if the patient presents with unexplained second- and third-trimester losses. Testing is **not** recommended for early first-trimester RPL since there is not proven relationship between early losses and these thrombophilias.

F Endocrinologic factors

1. Untreated or poorly controlled hypothyroidism may increase the risk of miscarriage.
2. **Poorly controlled insulin-dependent diabetes mellitus**, particularly with hemoglobin A1C (a measure of disease control) values above 8%, increases the risk of miscarriage and the risk of major congenital malformations in the fetus.
 - a. Risk of miscarriage is most likely due to the degree of hyperglycemia and maternal vascular disease.
 - b. No increased risk of miscarriage is seen with well-controlled diabetes mellitus.
3. Luteal-phase deficiency has been implicated in the cause of RPL. Progesterone is responsible for the progressive changes of the endometrium following ovulation. A lack in progesterone or progesterone activity has been associated with a short luteal phase and RPL.
 - a. This is diagnosed by a midluteal-phase progesterone level of less than 10 ng/mL.
4. Other endocrinopathies such as polycystic ovary syndrome (PCOS) and hyperprolactinemia have been implicated in RPL, however a causal role has not been established.

V

RPL EVALUATION OVERVIEW

In a couple with RPL, initial evaluation should focus on a thorough history and record review.

- A** Gestational ages of all miscarriages should be ascertained as well as any workup or treatment performed previously.
- B** In the initial evaluation, laboratory work including APS evaluation and thyroid-stimulating hormone should be obtained; other laboratories should be measured in accordance with the couple's individual medical history.
- C** Imaging of the uterus is important to evaluate the possibility of a müllerian anomaly or other anatomic cause.
- D** A karyotype is usually performed last because a translocation is far less common than other causes of RPL. However, a karyotype may be ordered at any point in the evaluation.
- E** It should be noted that even if one abnormality is discovered, a complete evaluation is still recommended given the possibility of a multifactorial etiology for the RPL.

VI

TREATMENTS FOR WOMEN WITH RPL

A Overview

1. Many women with RPL have a normal evaluation and therefore are classified as idiopathic.
2. Some treatments that have been targeted at this population have unsubstantiated efficacy and possible harm. This section will focus on treatments with proven benefit for patients falling into specific etiologies of RPL.
3. For those women with idiopathic RPL, counseling about the odds of a future successful pregnancy without treatment and supportive care should be emphasized.

B Treatments for anatomic causes

1. **Uterine septum** is the most common and most strongly associated defect with RPL and can be surgically removed. This is best accomplished by use of a **hysteroscope**, which allows the surgeon to visualize and resect the septum from its distal aspect to its proximal aspect.
2. For women with a **bicornuate uterus** or **uterine didelphys**, careful obstetric management is the preferred approach. A **metroplasty** is a surgical procedure to unify the cavities and reconstruct the uterus and can be performed when pregnancy outcomes have been particularly poor despite excellent and aggressive prenatal care in previous pregnancies. Unlike the septum resection, which is a minor surgical procedure, metroplasty is a major abdominal surgery.
3. For women with a **unicornuate uterus**, surgical options to prevent first-trimester miscarriage are limited. Metroplasty is not an option because these patients have only one developed uterine horn.
4. Fibroids implicated in RPL can be removed by a number of surgical techniques to restore a normal uterine cavity (see Chapter 28).
5. Intrauterine adhesions are removed surgically via hysteroscopy.
6. Patients should be counseled extensively before going forward with any surgical procedure for RPL. Surgical risks and potential benefits should be reviewed. A patient who has a metroplasty, for example, must have a cesarean section for all deliveries because the nature of the surgery makes labor and vaginal delivery extremely risky. For patients with particularly poor obstetric histories who decline surgery, are not surgical candidates, or have failed surgical treatment, the use of a **gestational carrier** who carries the pregnancy as a surrogate may be a consideration.

C Treatments for parental genetic abnormalities If it is determined that a member of the couple has a balanced chromosomal translocation, several options exist. Reproductive or medical genetic counseling can be extremely useful in managing these patients.

1. The couple could continue to try to conceive on their own. If one person is affected with a balanced translocation, there still exists the possibility of a spontaneous normal conception. However, rates of successful pregnancies in couples with a balanced translocation vary according to the specific translocation, and a successful pregnancy is *less* likely if the translocation is of maternal origin (approximately 25% if the woman carries the translocation and 40% if the male is the carrier).
2. **In vitro fertilization (IVF) and preimplantation genetic diagnosis (PGD)** in an attempt to select normal embryos for conception prior to transfer of embryos to the uterus
 - a. Oocytes are harvested from the female partner and combined with sperm outside the body.
 - b. Embryos that are generated from this process can be biopsied (usually a single cell from a 6 to 8 cell embryo) and evaluated for chromosomal abnormalities using fluorescence in situ hybridization.
 - c. Embryos with a normal karyotype can be selected and transferred to the uterus of the patient.
 - d. This technique is indicated for couples that have a specific chromosome abnormality implicated in RPL. It is not indicated to screen for chromosomally normal embryos prior to transfer in couples who have unexplained RPL (a technique referred to as preimplantation genetic screening).
3. Donor gametes can be used (egg donation if the female carries the translocation or sperm donation if the male is affected) in combination with fertility treatments.

D Treatment of antiphospholipid antibody syndrome Prior to treatment of antiphospholipid antibody syndrome, the diagnosis must be confirmed as outlined above.

1. Adequate treatment of antiphospholipid antibody syndrome requires that the affected individual receive subcutaneous heparin injections throughout her pregnancy. This treatment strategy reduces the likelihood developing placental microthrombi due to antiphospholipid antibodies. Heparin can be administered as unfractionated or low-molecular-weight heparin (neither form of heparin crosses the placenta). Some advocate the use of low-dose aspirin in conjunction with heparin (81 mg/d).

2. Long-term treatment with heparin can be unpleasant for patients and has potential risks (bleeding, osteoporosis, and heparin-induced thrombocytopenia).
3. Despite these drawbacks, the combination significantly improves the odds of a live birth in those treated (up to twofold increase in clinical trials).

E Treatment controversies As mentioned previously, several approaches (listed below) have been explored for women with unexplained RPL. None of these treatments has demonstrated efficacy in the treatment of RPL.

1. Low-dose **aspirin** in the absence of a diagnosis of APS.
2. Empiric **progesterone** supplementation after ovulation for a luteal phase defect.
3. Immunomodulation of the female partner using **intravenous immunoglobulin (IVIG)**. It has been postulated that an abnormal maternal immune response to the early conceptus may play a role in RPL and that IVIG could suppress this response.
4. Immunomodulation of the female partner through vaccination **with paternal leukocytes** (before reattempting conception) to sensitize the mother to the paternal components of the fetus. This therapy may increase the odds of miscarriage and its use for the treatment of RPL has been restricted by the FDA.

F Natural history/observation Many couples with unexplained RPL can be reassured that their odds of having a successful future pregnancy are reasonable even if no treatment is utilized. This is especially true if the couple has ever experienced a live birth. For instance, a woman with a history of three unexplained miscarriages and one prior liveborn infant has a 32% chance of the next pregnancy being a miscarriage—in other words, a 68% chance that the pregnancy will develop normally. Education and reassurance is an extremely important facet of the care provided to these couples.



Study Questions for Chapter 31

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A patient with a history of three miscarriages presents to your office. The only workup she has had done so far was a laboratory evaluation that showed the following results: lupus anticoagulant screen negative, anticardiolipin IgA high positive, IgG low positive, and IgM normal. What would you offer the patient next?

- ☐ A Discuss with her that she has APS and devise a treatment plan based on this diagnosis
- ☐ B Repeat antiphospholipid screen in 6 to 8 weeks
- ☐ C Start heparin and baby aspirin treatments immediately
- ☐ D Start baby aspirin with next pregnancy
- ☐ E None of the above

2. A couple with RPL gets karyotype analysis and the male partner is found to have a robertsonian translocation involving chromosomes 14 and 21. The female partner is normal. The next most appropriate step in the treatment of this couple is:

- ☐ A Offer IVF as an option for treatment
- ☐ B Discuss the role of donor gametes in treatment
- ☐ C Offer the couple IVF with PGD
- ☐ D Close observation with next pregnancy
- ☐ E Send the couple for a consult with a genetic counselor

3. A patient with a history of three miscarriages presents to your office. The only workup she has had done so far was a laboratory evaluation that showed the following results: lupus anticoagulant screen negative, anticardiolipin IgG high positive, and IgM normal. What would you offer the patient next?

- ☐ A Discuss with her that she has APS and devise a treatment plan based on this diagnosis
- ☐ B Repeat antiphospholipid screen in 12 weeks
- ☐ C Order an HSG
- ☐ D B and C
- ☐ E None of the above

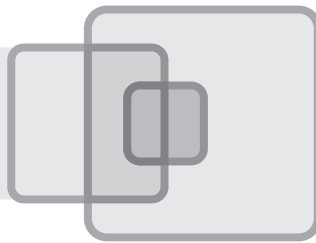
4. A couple presents to your office with a history of a full-term delivery by a cesarean section for breech presentation followed by three losses: a second-trimester loss at 14 weeks, a loss at 8 weeks, and a loss at 6 weeks. Her evaluation has included a negative APS screening, normal chromosome analysis on both the woman and man, and a pelvic ultrasound revealing a normal uterus with no obvious fibroids. The next step would be to:

- ☐ A Repeat APS screening greater than 12 weeks after the first screen
- ☐ B Screen for thrombophilias
- ☐ C HSG
- ☐ D Reassure the couple that since they have had a successful pregnancy, and the evaluation has been unremarkable, they should be able to have a healthy baby
- ☐ E Recommend a gestational carrier



Answers and Explanations

1. **The answer is E** [IV D]. The patient does not have APS based on these laboratory results. Anticardiolipin IgA being positive is not part of the diagnostic criteria, and the low-positive IgG is also not positive. There is no need to repeat these tests again. Since the patient does not have the syndrome, there is no need to initiate anticoagulant therapy, but alternative causes of her RPL should be sought.
2. **The answer is E** [IV C, VI C]. The couple should hear from an experienced geneticist or genetic counselor what the implications of their translocation are for their offspring (e.g., if the pregnancy survives and the fetus is affected with a trisomy) and the exact statistics with respect to odds of a normal pregnancy with no intervention. A discussion of donor egg, donor sperm, or IVF with PGD should occur with a reproductive endocrinologist who can explain and offer these treatments. Ideally these treatment possibilities should be discussed after the patient has been seen by a genetic counselor.
3. **The answer is D** [IV D]. In order to confirm the diagnosis of APS, either anticardiolipin antibodies or lupus anticoagulant screen must be significantly positive twice, with at least 12 weeks between positive tests. Of note, the same laboratory abnormality must be present each time. For instance, if this patient had a positive lupus anticoagulant screen and a normalized anticardiolipin IgG, this would not represent a positive result. In addition, if the full panel of laboratories for the antiphospholipid screen were negative, other etiologies for RPL must be sought. It is reasonable to schedule the patient for uterine imaging while waiting for the repeat antiphospholipid screen to rule in or out an anatomic cause of RPL.
4. **The answer is C** [II B 3]. The next best step is to evaluate the uterine cavity for a müllerian anomaly such as a uterine septum. Uterine septum has been implicated in second-trimester losses and first-trimester losses. However, many women with müllerian anomalies have successful pregnancies, but are at increased risk for fetal malpresentation requiring a cesarean section for delivery, as with this woman. A pelvic ultrasound is not reliable in detecting a uterine septum and further evaluation with HSG or hysteroscopy is indicated. If the HSG is normal then evaluation for APS and thrombophilias would be indicated. A gestational carrier would not be recommended unless the uterus was not capable of carrying a pregnancy, which is not the case here. Reassurance alone is only indicated if the complete evaluation is normal.



Family Planning: Contraception and Complications

COURTNEY A. SCHREIBER

I

CONTRACEPTIVE EFFICACY

The number of pregnancies per 100 woman-years is the number of pregnancies in 100 sexually active, fertile women who use a given method of contraception for 1 year. The expected pregnancy rate in women using no method of contraception is 85 pregnancies per 100 woman-years.

II

BARRIER METHODS

A Condoms One of the oldest surviving forms of birth control, condoms are effective, safe, and relatively inexpensive. Condoms are effective if used consistently.

1. **Mode of action.** Both female and male condoms act as physical barriers to semen.
2. **Advantages**
 - a. **Protection from sexually transmitted diseases (STDs)**
 - (1) **Latex condoms are the only contraceptive method that can protect against STDs** caused by herpes simplex virus, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Mycoplasma hominis*, *Trichomonas vaginalis*, *Treponema pallidum*, and HIV, but not human papilloma virus.
 - (2) **Natural, or nonlatex, condoms do not protect against most STDs** because they contain small pores that allow passage of microbes.
 - b. Easy accessibility
 - c. Few side effects
3. **Disadvantages**
 - a. Must be used in each act of intercourse
 - b. Requires cooperation of both partners
4. **Types of condoms**
 - a. **Female condoms** line the entire surface of the vagina and partially shield the perineum. They can be inserted up to 8 hours in advance but should be removed immediately after each act of intercourse. Female condoms should not be used in conjunction with male condoms.
 - b. **Male condoms** cover the glans and the shaft of the penis and must be used from the beginning to the end of each act of intercourse to be effective. Some condoms contain spermicidal agents. **Condoms impregnated with spermicide are no more effective than condoms alone.**
5. **Efficacy. Pregnancy rate** is 3 to 21 per 100 woman-years of use.

B Spermicides Creams, jellies, aerosol foams, nonfoaming and foaming suppositories, and vaginal films are commonly used with other forms of contraception, such as diaphragms, sponges, and condoms. Only about 3% of women use spermicides alone.

1. **Mode of action.** Spermicides serve as a **chemical barrier** to sperm. The **active agents** in spermicides (e.g., nonoxynol 9) disrupt the outer lipoprotein surface layer of spermatozoa, killing the sperm, decreasing their motility, or inactivating the enzymes needed to penetrate the ova.
2. **Advantages**
 - a. Increase the efficacy of vaginal sponges, diaphragms, and cervical caps
 - b. Available over the counter
 - c. No need for medical consultation
 - d. Few side effects
3. **Disadvantages**
 - a. Need for insertion with each act of intercourse
 - b. Limited duration of effectiveness
 - c. Possible increase in the risk of HIV transmission caused by disruption of vaginal epithelium. This increased risk appears to be dose dependent: people who use these products multiple times per day should be wary of this effect
4. **Efficacy. Pregnancy rate** is as much as 26 in 100 woman-years of use. As with mechanical barrier methods, efficacy depends on the couple's motivation to use spermicides correctly with every act of intercourse.

C Vaginal sponges

1. **Mode of action.** Vaginal sponges release spermicide during coitus, absorb ejaculate, and physically block the entrance to the cervical canal.
2. **Advantages**
 - a. Use for as long as 24 hours regardless of frequency of sexual intercourse
 - b. Few systemic side effects
3. **Efficacy. Pregnancy rate** is 40 in 100 woman-years of use in parous women and 20 in 100 woman-years of use in nulliparous women.

D Diaphragms

These dome-shaped contraceptives are 50 to 105 mm in diameter and are made of latex rubber. They rest between the posterior aspect of the symphysis pubis and the posterior fornix of the vagina, thus covering the anterior vaginal wall and the cervix.

1. **Mode of action.** Diaphragms act as physical barriers to sperm and are effective vehicles for holding spermicide over the cervix.
2. **Advantages**
 - a. Contraception for up to 6 hours after placement
 - b. Few side effects
3. **Disadvantages**
 - a. Need to keep in place for at least 6 hours after intercourse to ensure that no motile sperm are left in the vagina
 - b. Requirement for use with a spermicidal agent
 - c. Need to replace spermicide with each act of intercourse
 - d. Associated with an increased risk of urinary tract infections
 - e. Need to be fit by a clinician
4. **Efficacy. Pregnancy rate** is reported to be 5 to 10 in 100 woman-years of use.

E Cervical caps

These contraceptives are as effective as diaphragms but are more difficult to fit.

1. **Mode of action.** The cervical cap has the same mode of action as the diaphragm.
2. **Advantages**
 - a. Ability to leave in place up to 48 hours (compared to 6 hours with the diaphragm), regardless of number of acts of intercourse
 - b. Effectiveness without the addition of a spermicidal agent
3. **Disadvantages**
 - a. Need to keep in place for at least 6 hours after intercourse (same as the diaphragm)
 - b. Few physicians are trained in the placement and use of the cervical cap
4. **Efficacy. Pregnancy rate** is reported to be about 5 to 10 in 100 woman-years of use.

III

INTRAUTERINE DEVICES

These reversible methods of contraception are one of the most widely used throughout the world. Intrauterine devices (IUDs) are extremely effective in reducing the risk of pregnancy. The copper IUD (Para-Gard) and the progestin-only IUD (Mirena) are currently available in the United States. Both IUDs have multiple mechanisms of action but primarily act by preventing sperm mobility and oocyte fertilization. Evidence does not support the claim that IUDs are abortifacients.

A Types

1. The **copper-impregnated IUD** is approved for 10 continuous years of use. Evidence demonstrates that it is effective for 12 years.
2. The **progestin-impregnated IUD**, with levonorgestrel 20, is approved for 5 years and then must be replaced.

B Mode of action

1. **Copper-impregnated IUD**
 - a. **Copper itself acts as a spermicide.**
 - b. The IUD causes a local, sterile inflammatory reaction in the uterus, and the intrauterine environment becomes spermicidal.
 - c. The copper intensifies the inflammation in the uterine cavity, producing a lining that is unfavorable for implantation.
2. **Progestin-only IUD**
 - a. This IUD exerts its contraceptive effect locally on the endometrium and the cervix. Thickening of the cervical mucus makes the passage of sperm difficult, creating a barrier. Progestin alters the endometrium, rendering it unfavorable for implantation.
 - b. In addition, both uterine and tubal motility are impaired, thereby impairing sperm–egg interaction.

C Advantages These IUDs do not interfere with lactation and are not coitally dependent. IUDs and implants are the most effective reversible methods of contraception currently on the market.

1. **Copper-impregnated IUD**
 - a. As many as 12 years of continuous contraceptive efficacy from one IUD
 - b. Can be inserted at any time during the menstrual cycle
 - c. Resumption of fertility on removal
 - d. Can be used as emergency contraception up to 1 week after unprotected intercourse
2. **Progestin-only IUD**
 - a. As many as 5 years of continuous contraceptive efficacy from one IUD
 - b. Useful for treatment of menorrhagia (heavy menstrual bleeding) and dysmenorrhea (painful menses)
 - c. Resumption of fertility on removal of the IUD

D Disadvantages

1. **Insertion.** Although the copper-impregnated IUD may be inserted at any time during the menstrual cycle, the progestin-only IUD should be inserted within the first 7 days.
2. **Uterine perforation.** This complication occurs in about 1 in 1,000 insertions and should be suspected if the patient can no longer feel the string.
3. **Infection.** Risk is highest in the first 2 weeks after insertion because of possible introduction of bacteria into uterine cavity at the time of insertion. The risk of infection increases in women with a history of recent pelvic infection.

E Efficacy **Pregnancy rate** among users of either type of IUD is less than 2 to 3 in 100 woman-years of use.**F Contraindications**

1. **Known pregnancy**
2. Recent (less than 3 month) history of endometritis or purulent cervicitis
3. Distorted uterine cavity (increases expulsion rate)

G Pregnancy-related issues If a woman becomes pregnant with an IUD in place, it should be removed immediately because the IUD increases the risk of pregnancy loss and preterm labor. In addition, the risk of increased infection necessitates the removal of the IUD early in pregnancy.

1. The **spontaneous abortion rate** is about 50% if an IUD remains in place. The risk of miscarriage after removal in early pregnancy is about 20% to 30%. This is compared to the risk of first-trimester miscarriage in the general population of 20% to 25%.
2. In general, **ectopic pregnancy** is prevented by both the progestin-only and copper-impregnated IUDs. If a pregnancy does occur with an IUD in place, about 5% of women have an ectopic pregnancy.
3. The chance of a **premature birth** is 12% to 15% in pregnancies when an IUD is left in place. This is compared to the baseline risk of preterm labor of about 10% in the United States.

IV

PROGESTIN-ONLY METHODS

A Mode of action

1. Diminishing and thickening cervical mucus, thereby preventing sperm penetration
2. Producing a thin, atrophic endometrium, precluding implantation
3. Reducing the ciliary action of the fallopian tube, preventing sperm and egg transport
4. Diminishing the function of the corpus luteum
5. Occasional inhibition of ovulation by suppressing the midcycle peaks of luteinizing hormone (LH) and follicle-stimulating hormone (FSH)

B “Minipill” (norethindrone-only oral contraceptive). Less than 1% of oral contraceptive prescriptions in the United States are for this progestin-only oral contraceptive; however, typical use failure rates approximate the typical use failure rates of combined oral contraceptive pills. In women who desire a pill, but choose to/need to avoid estrogen, the progestin only pill is a suitable method.

1. Advantages

- a. No alteration of milk production and nearly 100% effectiveness in breastfeeding women
- b. Tolerance in women who are unable to take estrogen
- c. Independent of sexual intercourse

2. Disadvantages

- a. Irregular vaginal bleeding
- b. No protection against STDs
- c. Need for daily administration
 - (1) Progestin-only pills are taken continuously for 28 days without a pill-free interval. Because these pills have a dose of progestin that is very close to the threshold of contraceptive efficacy, they must be taken at approximately the same time each day.
 - (2) Suppressed ovulation occurs in only a proportion, and contraceptive efficacy depends on the other progestin-related mechanisms previously listed (see IV A).

3. **Efficacy. Pregnancy rate** is 5 in 100 woman-years of use. Consistent administration is necessary. A difference of a few hours may contribute to reduced contraceptive protection.

C Injectable progestin Medroxyprogesterone (Depo-Provera), the most commonly used injectable form of contraception, is given as a deep intramuscular or subcutaneous injection every 12 weeks. Menstrual patterns may be irregular during the first year of use; this is a common reason for discontinuation. Fifty percent of women develop amenorrhea within 1 year of use.

1. Advantages

- a. Effective for 12 weeks
- b. Independent of sexual intercourse
- c. Safe for use during breastfeeding
- d. Women on antiepileptic medications may have fewer seizures, and those with sickle cell disease may have fewer sickle cell crises

2. Disadvantages

- a. No protection against STDs
- b. Irregular bleeding and spotting
- c. Weight gain in certain populations (year 1, 5 lb; year 2, 16 lb)
- d. Prolonged return of fertility (median time from discontinuation to return of fertility, 8.5 months)

3. Efficacy. Pregnancy rate is less than 1 in 100 woman-years of use.

D Implantable progestin Implantable progestin-containing rods release hormones at a low but constant rate. Implanon is the single-rod implant currently available in the United States.

1. Advantages

- a. Effectiveness for up to 3 years
- b. Independent of sexual intercourse
- c. Almost immediate return of fertility after removal

2. Disadvantages

- a. Menstrual irregularity
- b. No protection against STDs
- c. Requires placement and removal by a trained provider

3. Efficacy. Pregnancy rate is less than 1 in 100 woman-years of use.**4. Specific types of implants**

- a. **Original form (Norplant)** is no longer manufactured. It consists of six implants each containing levonorgestrel, and is effective for up to 5 years. It is no longer available in the United States.

b. Implanon

- (1) This single implantable rod contains 3-keto-desogestrel, a progestin that is more potent than levonorgestrel. Studies have shown that serum hormone concentrations remain adequate for at least 3 years. Implanon users have a lower incidence of prolonged or irregular menstrual bleeding compared with users of Norplant; however, the incidence of oligomenorrhea (infrequent menses) and amenorrhea is higher.

E Progestin-only IUD (see III B)**V****COMBINATION ORAL CONTRACEPTIVE PILLS**

A Composition Combination oral contraceptive pills (OCPs) contain various amounts of estrogen (ethinyl estradiol) and one of a variety of progestins. The current preparations contain low doses of estrogen (usually 20 to 35 µg per pill). Most are taken for 21 days, with 1 week between pill packs, in either monophasic or triphasic combinations. Continuous use with intermittent menstrual withdraw (four menses a year) is becoming more widespread.

B Mode of action The primary mechanism is inhibition of the LH surge.

- 1. Suppression of ovulation
- 2. Thickening of the cervical mucus, resulting in ineffective sperm migration
- 3. Alteration of tubal motility
- 4. Alteration of endometrium to make it thin and inactive, thus hampering implantation

C Efficacy **Pregnancy rate** is 5 in 100 woman-years.

D Current controversies regarding complications**1. Venous thromboembolism (VTE)**

- a. Estrogen causes an increase in serum levels of several clotting factors, especially factor VII. Antithrombin III levels fall within 10 days of starting OCPs.
- b. The incidence of both superficial and deep vein thromboses is increased in OCP users. Risk increases as estrogen dose increases.

- c. Despite these risks, it is still safer for a woman to use OCPs than to become pregnant. The **attributable risk**, or the number of venous thromboembolic events attributable to estrogen in OCPs, is approximately 6 in 100,000 woman-years. The estimated risk in pregnant women is 20 in 100,000 woman-years.
 - d. Initial epidemiologic studies reported that women using **third-generation** (those that contain gestodene or desogestrel) OCPs have increased rates of venous thromboembolism compared with those using **second-generation** (containing norethindrone and levonorgestrel) OCPs. Additional studies demonstrated an inconsistent and weak association between OCPs and venous thromboembolism (strength of association, 0.7 to 2.3).
 - e. Women with **inherited thrombophilias** who take OCPs have an increased risk of thromboembolism. The risk of thrombosis with OCP use is six times higher in **carriers of antithrombin and protein C and protein S defects**. The odds of having a venous thromboembolism event are ten times higher in OCP users than in nonusers in carriers of the **factor V Leiden** mutation and seven times higher in carriers of the **prothrombin G20210A mutation**. Patients with a personal or family history of deep venous thrombosis or pulmonary embolus should be screened for these thrombophilias prior to starting OCPs. It is not necessary to screen all potential users of OCPs.
2. **Cardiovascular disease**
 - a. There is no evidence to support an increased or decreased risk of **myocardial infarction** resulting from past or current use of OCPs. The strength of association between OCP use and **stroke** is weak, with an odds ratio of 1.1:1.8 (most 95% confidence intervals cross 1.0).
 - b. However, a **synergistic effect** exists **between OCPs and smoking** as causes of cardiovascular events. **Heavy smoking, hypertension, severe diabetes mellitus with vascular complications, and obesity** (more than 50% above ideal body weight) are **independent** risk factors for cardiovascular disease. Women older than 35 years of age are at the highest risk for a cardiovascular event. However, women older than 35 years with no risk factors can safely use OCPs.
 3. **Hypertension**. Plasma renin activity, angiotensin levels, aldosterone secretion, and renal retention of sodium are all increased in OCP users. The resulting hypertension in a small number of OCP users may represent the failed suppression of plasma renin activity that occurs with elevated levels of angiotensin. The length of OCP use appears to relate to the development of hypertension, which develops in approximately 5% of users after 5 years of use. Normotensive levels return in almost all women who developed hypertension while taking OCPs when the contraception is discontinued.
 4. **Liver tumor**. An association between the use of OCPs and the subsequent development of a rare liver tumor, **hepatocellular adenoma**, has been reported. The associated risk increases when OCPs have been used for 5 years or more. Tumor development occurs at a rate of 3 in 100,000 woman-years of use.
 5. **Neoplasia**
 - a. **Breast cancer**
 - (1) Progestins antagonize the stimulating effect of estrogen on breast tissue. The incidence of breast cancer has remained fairly constant during the past 15 to 20 years despite widespread use of OCPs.
 - (2) A **small but statistically significant increase in risk of breast carcinoma exists in current (relative risk, 1.24) and recent** users (relative risk, 1.16) of OCPs, but not in past users.
 - (a) This increased risk equates to a small increase in the actual number of new cases of breast cancer, and it disappears after 10 years of use.
 - (b) **Cancers diagnosed** in recent or current OCP users **are not advanced and tend to be localized** compared with OCP nonusers.
 - (3) Patients with a family history of breast cancer have no additional risk.
 - b. **Endometrial cancer**. Progestins reduce the stimulating effect of estrogen and prevent the normal proliferative endometrium from progressing to hyperplasia, thus **decreasing the risk of endometrial cancer by 50%** (see V E 2).
 - c. **Ovarian cancer** (see V E 1)

E Noncontraceptive benefits

1. **Ovarian cancer.** OCPs suppress ovarian activity and inhibit ovulation; the interruption of a significant number of ovulatory cycles in oral contraceptive users may lead to a decreased incidence of ovarian cancer.
 - a. Users of OCPs are less likely to develop ovarian cancer than those who have never used OCPs. An average decrease of 40% in the likelihood of ovarian cancer is seen in women who have taken OCPs at some time. Protection is provided after as little as 3 to 6 months of use and persists for at least 15 years after discontinuation. Recent data also suggest that OCPs serve as primary prevention for women at risk for hereditary ovarian cancer.
 - b. In particular, the risk of ovarian cancer is **significantly reduced in current and past users** of OCPs. This risk reduction increases as the period of OCP use increases. Women at increased risk for epithelial ovarian cancer may benefit from OCP use.
2. **Endometrial cancer.** Users of OCPs have a 50% reduction in endometrial cancer compared with those who have never used OCPs. Risk is reduced with longer use of pills. The actual duration of protection is unknown but lasts for a minimum of 15 years.
3. **Benign breast disease.** Fibrocystic change and fibroadenoma development are significantly reduced with OCP use. Larger amounts of progestin and longer periods of use decrease the risk of benign breast disease. The risk is lowest in current OCP users.
4. **Ectopic pregnancy.** The contraceptive effect of OCPs prevents ectopic pregnancy. The protection rate is 90% in current OCP users.
5. **Iron deficiency anemia.** OCPs decrease menstrual blood loss and regulate menstrual bleeding, thus decreasing likelihood of iron deficiency anemia. This action benefits both past and current OCP users.
6. **Pelvic inflammatory disease (PID).** OCPs protect against only those patients with PID who require hospitalization. At least 12 months of OCP use is necessary, and protection is limited to current users. No protection against lower genital tract infections (e.g., cervicitis) and tubal infertility is evident.
7. **Dysmenorrhea.** OCPs improve primary dysmenorrhea. OCPs have also been shown to improve dysmenorrhea caused by endometriosis.
8. **Hirsutism and acne.** OCPs improve hirsutism and acne caused by hyperandrogenism by decreasing production of androgens by the ovary and adrenal and increasing sex hormone-binding globulin production by the liver.

F New combination OCP preparations

1. Packaging to allow continuous use with menstrual withdrawal every 3 months instead of monthly.
2. An OCP containing ethinyl estradiol with a new progestin, drospirenone, which is an analog of spironolactone, an androgen receptor blocker used for hirsutism.

VI**OTHER COMBINATION HORMONAL METHODS**

A Contraceptive vaginal ring (NuvaRing). This contraceptive device consists of a 5.4-cm flexible ring made of ethylene vinyl acetate copolymer containing ethinyl estradiol and etonogestrel. The ring is inserted into the vagina and the hormones are absorbed into the systemic circulation.

1. **Use.** The vaginal ring is worn continuously for 3 weeks and then discarded; a new ring is inserted into the vagina 1 week later. If the ring is left in place for more than 4 weeks, its contraceptive efficacy may be reduced.
2. **Mode of action** is similar to that of combined OCPs (see V B).
3. **Advantages**
 - a. Beginning of contraceptive effect within the first day of use
 - b. Inserted by the user; does not need to be fitted
 - c. Does not need to be removed for sexual intercourse
 - d. Rapid resumption of fertility on discontinuation

- e. Fewer side effects (e.g., weight gain, acne, bleeding irregularities, and breast tenderness) than combined OCPs
- f. Does not require daily attention
- 4. **Disadvantages** include no protection against STDs.
- 5. **Efficacy** is similar to that of combined OCPs.

B Transdermal patch (Ortho Evra). The once-weekly contraceptive patch releases norelgestromin, the active metabolite of norgestimate, and ethinyl estradiol daily to the systemic circulation.

1. **Use.** Typical use includes placement of the patch on the same day of each week for 3 consecutive weeks followed by a patch-free week.
2. **Mode of action** is similar to that of combined OCPs (see V B).
3. **Advantages**
 - a. Maintenance of normal activity, including bathing, swimming, and heavy exercise while using the patch
 - b. Noncontraceptive benefits. The noncontraceptive effects of transdermal administration have not yet been studied but are expected to be similar to those of combined OCPs
 - c. Independent of sexual intercourse
 - d. Rapidly reversible on discontinuation
 - e. Does not require daily or coital attention
4. **Disadvantages** include no protection from STDs.
5. **Efficacy** is similar to that of combined OCPs.
6. **Controversies.** The FDA recently issued a warning that the Ortho Evra patch may be associated with a greater risk of VTE than is found with combination OCPs. One published study reported no significant difference in risk of VTE with the two methods of contraception. A second study, not yet published, reported a significantly higher risk with the patch compared with the oral contraceptive. In response to the second study, the FDA mandated a labeling change warning of increased risk of VTE with the patch. The attributable risk remains low.

VII EMERGENCY CONTRACEPTION

The primary **advantage** of this type of contraception is that it has no medical contraindications except previously established pregnancy. Its primary **disadvantage** is lack of protection against STDs. Methods of emergency contraception include the combined and progestin-only contraceptive pills, and copper-impregnated IUD.

A Overall mode of action A single mechanism of action has not yet been established. Emergency contraception probably prevents pregnancy by causing anovulation or delaying ovulation. An effect on the endometrium preventing implantation has also been suggested.

B Overall efficacy The efficacy declines with increasing delay between episode of unprotected intercourse and initiation of treatment. Among the oral contraceptives, the progestin-only method is more effective in preventing pregnancy than the combination-pill, or Yuzpe, method (85% effective vs. 57%). The copper-impregnated IUD is significantly more effective than the use of hormonal emergency contraception, which has a failure rate of 0.1%.

C “Morning-after pill”

1. **Combination method.** The most common regimen involves four tablets that are a combination of ethinyl estradiol and norgestrel, given as two tablets twice over 12 hours. The necessary **minimum effective dose** of ethinyl estradiol and norgestrel is 100 µg and 1.0 mg, respectively (**Yuzpe method**).
2. **Progestin-only method.** The most common regimen is levonorgestrel, 0.75 mg, taken 12 hours apart. The necessary **minimum dose** of levonorgestrel is 1 mg. A single dose of 1.5 mg has been shown to be even more effective than the two doses of 0.75 mg.
3. Prepackaged, commercially available emergency hormonal contraception

- a. **Plan B** is a **progestin-only method** that consists of two tablets, each containing 0.75 mg of levonorgestrel, and detailed instructions for both physicians and patients.
 - b. This preparation is available over the counter in the United States for women over the age of 18 years.
 - 4. **Use.** The “morning-after pill” is best taken within 120 hours of unprotected coitus; use within 24 hours increases efficacy: the sooner the better.
 - 5. **Side effects.** Most common side effects include nausea (about 50% of women) and vomiting (about 20% of women). An antiemetic is often needed with combination pills but *not* with progestin-only pills.
- D** The **copper-impregnated IUD** can be used as an alternative method. It should be inserted up to 5 to 7 days after ovulation to prevent pregnancy. The copper IUD is significantly more effective than the use of hormonal emergency contraception; the failure rate is 0.1%. Its expense may preclude use.

VIII

NATURAL FAMILY PLANNING

This contraceptive method entails avoiding pregnancies by abstaining from sexual intercourse during the fertile phase of the menstrual cycle. Drugs, devices, and surgical procedures are not used. Coitus is limited to before and after the fertile period each month.

- A Fertility awareness** Women are most fertile several days around the time of ovulation.
- 1. Fertility status can be determined by charting basal body temperature, maintaining a menstrual calendar, and monitoring changes in cervical mucus.
 - 2. Fertility determination depends on a couple's ability to identify and interpret signs of fertility.
- B Basal body temperature** is the temperature of the body at complete rest after a period of sleep and before normal activity, including eating.
- 1. The basal body temperature exhibits a biphasic pattern during an ovulatory cycle (i.e., it is lower in the first half of the cycle, increases at the time of ovulation, and remains higher for the rest of the cycle).
 - 2. The basal body temperature **increases 0.4 to 1.0°F during the postovulatory phase** of the cycle because the secretion of progesterone has a thermogenic effect.
 - 3. **As an indicator of fertility**, the basal body temperature can detect only the end of the fertile phase because the temperature elevation is detected after ovulation.
 - 4. **To avoid pregnancy**, a couple must restrict sexual intercourse from the end of menses to 1 to 2 days after the temperature elevation.
- C Menstrual calendar calculations**
- 1. Calculations are based on the following assumptions:
 - a. Ovulation occurs on day 14 (plus or minus 2 days) before the onset of menses.
 - b. Sperm remain viable for about 5 days.
 - c. The ovum survives for about 1 day.
 - 2. Lengths of previous cycles give an estimate of when to avoid intercourse during a current cycle.
- D Cervical secretions**
- 1. Varying concentrations of estrogen and progesterone affect the quantity and quality of cervical mucus.
 - 2. Secretions **during the fertile period are abundant, clear or white, slippery, and stretchy**. Ovulation occurs within 1 day before to 1 day after the appearance of this discharge.
 - 3. **After ovulation**, as progesterone levels increase, cervical secretions become **thick, cloudy, and sticky**.
 - 4. It is presumed that the **fertile period** begins when cervical secretions are first noted until 4 days past the peak of the slippery discharge. **To avoid pregnancy, couples should abstain from intercourse during the fertile period.**

E Advantages

1. Acceptance by some religions that disapprove of other methods of contraception
2. Involvement of both partners
3. Minimal cost
4. No medical consultation needed

F Disadvantages

1. No protection against STDs
2. Difficulty of use with irregular menses
3. Ovulation can occur unpredictably even in women with generally regular cycles

G Efficacy **Pregnancy rate** among women using natural family planning is 10 to 23 in 100 woman-years of use.

IX**SURGICAL STERILIZATION**

These procedures have become one of the most widely used methods of contraception. Both tubal ligation and vasectomy are designed to be permanent. Depending on the technique used, tubal sterilization has a failure rate during the first year of 0.7% to 5.4%. Different techniques include cauterization of the mid-isthmic portion of each tube, using clips, or rings to occlude the tube. These can be done laparoscopically. Resection of portion of fallopian tubes can be done postvaginal delivery through a small subumbilical incision. Counseling is essential; nearly 6% of women regret their decision, but this is much more common in women younger than 30 years. Vasectomy has a failure rate during the first year of 0.1%.



Study Questions for Chapter 32

Directions: Match the description below with the best method of contraception. Each answer may be used once, more than once, or not at all.

QUESTIONS 1–4

- ☐ A Depot-medroxyprogesterone acetate
- ☐ B Progestin-only pill (minipill)
- ☐ C Combination birth control pill
- ☐ D Progesterone IUD
- ☐ E Vaginal contraceptive ring

1. A 24-year-old woman, gravida 3, para 3, who just delivered a healthy boy and is breastfeeding him. She is a successful model and cannot tolerate excessive weight gain. She has never been able to remember to take a pill daily.
2. A 29-year-old nulliparous woman who has factor V Leiden deficiency and a bicornuate uterus. She is a librarian who exercises 6 days a week in order to maintain her physique. She has had several tumultuous relationships this year. She tries to use condoms in addition to this contraceptive method to prevent STDs.
3. A 28-year-old nulliparous physician who has a history of major depression. She is on call in the hospital every 4 days and sometimes forgets to take her antidepressant medication. She has been in a new relationship for the past 2 months. She always uses condoms in addition to this contraceptive method to prevent STDs.
4. A 26-year-old woman, gravida 4, para 4, is happily married. She has regular periods that last 9 to 10 days, are extremely heavy, and are associated with severe cramping. She is fairly sure she has completed childbearing.

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

5. Your 24-year-old multiparous patient is interested in long-term contraception, but is concerned that the copper IUD acts as an abortifacient. The best guidance you could give her is:
 - ☐ A She should not use the copper IUD because its main mechanism of action is as an abortifacient
 - ☐ B The main way in which the copper IUD prevents pregnancy is by acting as a spermicide
 - ☐ C Tubal ligation is a more effective long-term contraceptive than an IUD, so she should consider that instead
 - ☐ D IUD is associated with a high rate of infection (pelvic inflammatory disease)
6. A 25-year-old woman, gravida 1, para 0, therapeutic abortions (TAB) 1, presents to the emergency department and is being evaluated for date rape, which occurred 12 hours ago. She says that the rapist forced himself onto her and had time to ejaculate inside her. She has no past medical history. In addition to prophylactic treatment for STDs, complete rape evaluation, and counseling, the most effective and widely available management to prevent pregnancy is:
 - ☐ A Ethinyl estradiol and norgestrel, two tablets now and two in 12 hours
 - ☐ B Ethinyl estradiol and norgestrel, two tablets now and two in 12 hours, and prochlorperazine
 - ☐ C Plan B 150 mg now
 - ☐ D Levonorgestrel, 0.75 mg now and another in 12 hours

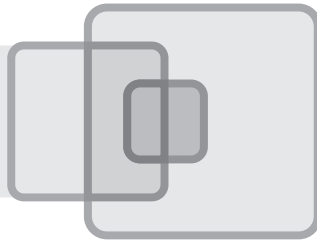


Answers and Explanations

1. **D** [IV B], 2. **B** [IV B], 3. **E** [VI B], 4. **D** [III C 2]. Women who are breastfeeding should use progestin-only contraceptive methods so as to not affect their quantity and quality of breast milk. This first patient cannot tolerate depot-medroxyprogesterone acetate because it is associated with 5-lb-per-year weight gain in a subpopulation of women. The progestin-only pill may not be ideal since she cannot remember to take pills daily and the efficacy of this pill is dependent on taking the pill at the same time each day. Therefore, the IUD would be the best option. The second patient would benefit from the progestin-only pill because (1) she should avoid estrogen-containing contraceptive methods (combination pills or patch) because of her inherited thrombophilia; (2) she should avoid depot-medroxyprogesterone acetate because she is concerned with weight loss; and (3) she is not a candidate for an IUD because she has an abnormal uterine cavity. The third patient has depression, and depot-medroxyprogesterone acetate has been associated with major depression. She may forget to take any form of daily (pill) contraceptive because of her busy schedule. The IUD is not contraindicated in nulliparous women, but does require insertion, which may be uncomfortable for this patient. Therefore, the vaginal contraceptive ring is the best option. The fourth patient would benefit from the progestin-releasing IUD because her dysmenorrhea and menorrhagia would improve. She is also in a monogamous relationship, which makes her the perfect candidate for this form of contraception.

5. **The answer is B** [III B]. The copper IUD predominantly gets its efficacy from the spermicidal action of the copper. The IUD is as effective as a tubal ligation, does not have to be removed for 12 years, and is reversible. It is not associated with a high rate of PID.

6. **The answer is C** [VII B and VII C 3 a]. The progestin method is more effective in preventing pregnancy than the combination pill method. Taking both pills at once increases the efficacy; therefore, taking Plan B 150 mg at once is a better choice. The combination method is associated with severe nausea and should be used with anti-nausea medication. The copper IUD is even more effective than the progestin method, but it is not in the answer choices.



Sexually Transmitted Infections

ANN HONEBRINK

I

INTRODUCTION

Sexually transmitted infections (STIs) are among the oldest described conditions in medical history. References to gonorrhea can be found in the Bible. The number of protozoan, bacterial, viral, and ectoparasitic infections that have been identified as sexually transmitted has continued to increase since biblical times.

II

GENERAL CONSIDERATIONS

A **Control of STIs** is currently a major public health concern, especially because there is a growing appreciation that individuals infected with other STIs are more susceptible to infection with HIV. In the developed world, the United States has the highest incidence of STIs, with an estimated cost of more than \$17 billion per year.

1. **Screening of at-risk individuals** and promoting preventive practices are the mainstays of prevention. All STIs have similar risk factors that should prompt screening and include:
 - a. Young age
 - b. Multiple sexual partners/recent new sex partner
 - c. Failure to use barrier contraception
 - d. Early onset of sexual activity
 - e. History of prior STI
 - f. Illicit drug use
 - g. Contact with sex workers
 - h. Men having sex with men (MSM)
 - i. History of current STI should prompt screening for HIV and other concomitant STIs
2. **Prevention of STIs.** These factors apply to all patients with STI
 - a. Counseling at-risk individuals on safer sex practices, condom use
 - b. Screen and presumptive treatment of sexual partners of infected persons
 - c. Completion of both patient and partner(s) treatment before resumption of sexual relations
 - d. Vaccination currently available for hepatitis A, B, and human papillomavirus (HPV)
 - e. Male circumcision has been shown to decrease transmission of STIs and HIV from women to men, but it has not been shown male to female transmission is decreased
 - f. Adolescent counseling, screening, and treatment strategies should include the special needs of this age group

III

BACTERIAL SEXUALLY TRANSMITTED DISEASES

A **Gonorrhea** The cause of this STD is the Gram-negative diplococcus *Neisseria gonorrhoeae*. Humans are the only natural host of this bacterium, which has a predilection for **columnar and transitional epithelium**. In **women**, who often have mild or no symptoms, gonorrhea may cause cervicitis, urethritis, pelvic inflammatory disease (PID), and acute pharyngitis. In **men**, who are

often symptomatic, infection can cause urethritis, prostatitis, and epididymitis. Systemic sequelae later develop in both men and women. In **newborns**, exposure at birth results in a 30% to 40% chance of subsequent infection including gonococcal conjunctivitis (ophthalmia neonatorum which used to be the most common cause of blindness in the United States), infection of the joints, serious sepsis and meningitis.

1. Epidemiology

a. In 2008, 336,742 cases of gonorrhea were reported to the centers for disease control and prevention (CDC). This figure is believed to represent about half of the total infections in the United States. Infection rates have fallen since the mid-1970s but seem to have plateaued since the mid-1990s. **Approximately 75% of reported cases occur among 15- to 29-year-old individuals. While in the past rates of reported infection had been higher in men than women, in 2008 a slightly higher rate of infection has been found in women (119.4/100,000) than in men (103/100,000).** Rates of infection are greater for African Americans than for whites. Coinfection with chlamydia is common and gonorrhea infection increased the risk of acquiring HIV.

b. **Transmission** from men to women by sexual contact is likely to result in infection after a **single exposure and increases after multiple exposures.** Highest rate of disease is seen in 15 to 24 year olds.

2. **Clinical presentation.** In both sexes, when symptoms occur, they usually appear 2 to 5 days after exposure but may not be evident for 30 days. Of women infected with gonococcal cervicitis, 50% are asymptomatic, while only 10% of infected men are asymptomatic. Symptoms include:

- a. Mucopurulent discharge, as occurs in acute cervicitis in women and urethritis in men
- b. Lower abdominal pain, anorexia, and fever, as is characteristic of acute PID; gonorrheal infection has been shown to be the initiating infection in 40% of cases of PID and PID has been shown to occur in 10% to 40% of women with gonococcal cervicitis. Perihepatitis can also occur because of peritoneal spread of infection
- c. Dysuria (men and women) caused by underlying urethritis
- d. Pharyngitis (in men and women after oral contact with an infected penis)
- e. Proctitis in male or female recipients of anal intercourse
- f. **If untreated, disseminated gonococcal infection occurs in 1% to 3% of infected patients and is more common in men than in women**

- (1) Arthritis (both tenosynovitis and purulent, mono- or polyarticular)
- (2) Pustular or vesicopustular skin lesions may accompany arthritis
- (3) Septicemia
- (4) Endocarditis, meningitis, and osteomyelitis (all rare)

g. Other sequelae

- (1) Women: tubal damage with pelvic infection leads to increased risk of infertility, and ectopic pregnancy. Tubo-ovarian abscesses can form as a sequelae of pelvic infection. Chronic pelvic pain is also a potential consequence of gonorrheal pelvic infection.
- (2) Men: risk of epididymitis with subsequent infertility and urethral scarring, as well as chronic prostatitis.
- (3) Both sexes: three to five times increased risk of acquisition of HIV infection with HIV exposure.

3. **Diagnosis.** Exact diagnosis depends on identification of *N. gonorrhoeae* by one of several methods:

- a. **Thayer-Martin culture medium.** This technique is selective for *N. gonorrhoeae*. Culture specimens must be incubated at 35 to 36°C in a 5% CO₂ atmosphere. This culture technique is highly sensitive and specific, inexpensive, and suitable for use for specimens taken from a variety of body sites (e.g., rectum, pharynx, cervix, and urethra). In addition, cultured organisms can be tested for antimicrobial sensitivity. While culture is 100% specific, sensitivity has been shown to be decreased to 65% to 85% in asymptomatic women. Culture is preferred for children or other individuals in which the diagnosis may have legal implications.
- b. **Gram stain**, looking for Gram-negative diplococci in polymorphonuclear leukocytes. This test is useful in male intraurethral and neonatal conjunctivitis specimens.
- c. **Nucleic acid amplification test (NAAT).** These tests, which use nucleic acid sequences unique to a specific organism for identification, do not require viable organisms to produce a positive result. Results are available (within hours) more quickly than culture (48 hours).

The NAAT technology uses polymerase chain reaction (PCR), strand displacement amplification, or transcription-mediated amplification to amplify organism-specific DNA or RNA sequences. These tests have a sensitivity over 95% in endocervical specimens using culture as a standard. The NAAT can also be used on male urethral specimens, female vaginal specimens, and male and female urine specimens but is not reliable on pharyngeal or rectal specimens. Testing is also possible from liquid-based Pap smear specimens. Sensitivity has been reported to be lower in female urine when compared to endocervical specimens.

4. **Treatment.** Because coinfection with *Chlamydia trachomatis* occurs often in patients infected with *N. gonorrhoeae*, consideration should be given to treatment plans that cover both organisms, especially in populations at high risk for STDs. Emergence of antibiotic-resistant strains of gonorrhea has narrowed treatment options.
 - a. For **uncomplicated gonococcal infection of the urethra, cervix, and rectum**, all recommended regimens involve a **single treatment**, which is important in increasing compliance. CDC-recommended regimens include:
 - (1) Ceftriaxone 125 mg intramuscularly or cefixime 400 mg orally in a single dose. In some areas mean inhibitory concentration (MIC) for ceftriaxone have risen and the recommended dose is now 250 mg IM.
 - (2) **In 2007, the CDC stopped recommending treatment with quinolones** since high rates of quinolone resistance have been found across the United States.
 - (3) **Alternative regimen: spectinomycin** 2 g is available outside the United States but is no longer available in the United States. Other single-dose cephalosporin treatments available include cefixime 500 mg IM, cefixime 2 g IM with probenecid 1 g orally, or cefotaxime 500 mg IM.
 - (4) **Azithromycin** 2 g orally (single dose) is also effective, but expense and gastrointestinal side effects at this dose limit use. Also, necessary minimal inhibitory concentrations needed to treat gonorrhea have been rising since 1999. This regimen is not part of the CDC treatment recommendations.
 - (5) Aggressive screening and treatment of pregnant women as well as prophylactic treatment of newborns with erythromycin or tetracycline ophthalmic ointment are the mainstays of prevention of neonatal conjunctivitis.
 - b. Since coinfection with chlamydia is common, treatment for chlamydia in conjunction with treatment for gonorrhea should be considered unless chlamydia infection has been ruled out. When treating for presumed or proven coinfection with *C. trachomatis*, it is necessary to add either azithromycin 1 g orally (single dose) or doxycycline 100 mg orally twice daily for 7 days. (Doxycycline should not be used in pregnant women or in children.)
 - c. More complex, inpatient treatment is required for patients with PID (see Chapter 34); infected infants; and individuals with disseminated gonorrhea, gonorrheal meningitis, or endocarditis.
5. **Follow-up.** Although tests of cure are no longer necessary when patients are treated successfully with the previously described regimens (see II A 4), tests for reinfection should be considered in individuals at high risk. When using **nucleic acid tests**, remember that the test **can remain positive for up to 3 weeks after treatment**; live organisms need not be present for a positive test. Repeat testing is also warranted in individuals with persistent symptoms.

B Chlamydia *Chlamydia*, a genus of obligatory Gram-negative intracellular bacteria, is the pathogen in a broad spectrum of infections. *C. trachomatis* (serotypes B, D, E, F, G, H, I, J, and K) is the obligate intracellular bacterium that causes sexually transmitted chlamydial genital infection.

1. **Epidemiology.** Chlamydia is the **most commonly reported STI and the most common bacterial STI** in the United States; 1,210,523 cases were reported in 2008. It is estimated that more than 4,000,000 cases actually occur annually. Infection rates have increased from 35 per 100,000 to 401.3 per 100,000 from 1986 through 2008. Chlamydia is most commonly diagnosed in adolescents and young adults up to 25 years of age but can also occur in older, at-risk individuals. Infection rates are higher in African American women. Detection rates in women are three times that in men, probably reflecting more aggressive screening in women. Coinfection with *N. gonorrhoeae* is common, and susceptibility to HIV infection in individuals with chlamydia is estimated to be increased three- to fivefold. Routine screening of asymptomatic, at-risk individuals has been

shown to decrease occurrence of PID by up to 60%. Screening for chlamydia is recommended for all pregnant women as well as sexually active women 25 and under and older women with risk factors such as multiple sexual partners.

2. Clinical presentation

- a. Women are asymptomatic 75% of the time.
- b. In symptomatic women, **mucopurulent cervicitis** can be demonstrated.
- c. Symptoms of **urethritis** and **pyuria** and a **negative urine culture** in sexually active women suggest a chlamydial infection. Incubation period from exposure to symptoms is 7 to 14 days.
- d. **Fever** and **lower abdominal pain** suggest PID, which occurs in as many as 40% of women with untreated chlamydia (see Chapter 34). These infections may be more insidious and protracted in duration than those associated with gonococcal PID. Perihepatitis and tubo-ovarian abscess can also occur with chlamydial PID.
- e. Although 50% of chlamydial infections in men are asymptomatic, urethritis may occur.
- f. In exposed infants, *C. trachomatis* may cause conjunctivitis and pneumonia.

3. Diagnosis

- a. **Culture.** Testing should be done from the endocervix in women and urethra in men. Culture for chlamydia is a highly specific technique and has been the gold standard for diagnosis of chlamydia. Culture should be used in children and in other cases that have potential legal implications. Antimicrobial susceptibility testing can be performed on isolates. However, culture techniques involving tissue culture are expensive and technically challenging, and the results are difficult to standardize.
 - b. **Nucleic acid amplification techniques (NAAT)** as described above. Urine testing is possible to detect genital infection in both men and women; however, endocervical sampling in women may be more sensitive. With a sensitivity of 80% to 93% and a specificity of 99%, NAATs have become the most utilized tests for chlamydia testing. However, it should be noted that when the prevalence in a population is less than 2%, a positive test only has a positive predictive value of 63% and therefore should be interpreted with care.
4. **Treatment.** The therapy for PID is discussed in detail in Chapter 34. Treatment for uncomplicated cases of urethritis and cervicitis includes:
- a. **Doxycycline** 100 mg orally twice daily for 7 days (contraindicated in pregnancy)
 - b. **Azithromycin** 1 g orally in a single dose
 - c. **Ofloxacin** 400 mg orally twice daily for 7 days (contraindicated in pregnancy)
 - d. **Erythromycin base** 500 mg or erythromycin ethylsuccinate 800 mg orally four times daily for 7 days
 - e. **Levofloxacin** 500 mg orally for 7 days (contraindicated in pregnancy)
 - f. **Ampicillin 500 mg orally three times a day for 7 days is an alternative recommended regimen for pregnant women**

5. Follow-up

- a. Retesting for cure may not be necessary after treatment with single-dose azithromycin or a complete course of doxycycline. In fact, retesting using nucleic acid technology less than 3 to 6 weeks after treatment may yield false-positive results in adequately treated individuals because nucleic acid technology does not rely on live organisms to produce a positive test.
 - b. However, retesting is advisable when reinfection is suspected and compliance with medication is not certain, especially in cases in which symptoms persist. Because reinfection with chlamydia is common in studies of previously infected women, the CDC recommends that rescreening be considered 3 to 4 months after treatment. In addition, test of cure at 3 or more weeks after treatment is recommended when erythromycin (commonly used in pregnancy) is used for treatment.
 - c. Evaluation for other STIs, especially HIV and gonorrhea is indicated.
6. **Sequelae.** Complications may include PID with sequelae of chronic pelvic pain, ectopic pregnancy, and infertility.

C Chancroid The Gram-negative coccobacillus *Haemophilus ducreyi* causes this genital ulcerative disease. *H. ducreyi* is a highly infectious Gram-negative rod.

1. Epidemiology

- a. Chancroid is rare in the United States but common worldwide. In sub-Saharan Africa, chancroid is the major cause of genital ulcers. In 2008, only 25 cases of chancroid were reported to the CDC in the United States. However, it is probably underdiagnosed and underreported. Trauma facilitates entry into mucosal vulvar tissues in women. The incubation time is 3 to 5 days and there is a 70% chance of infection after exposure. Cases are reported more commonly in men than women. When diagnosed in women in the United States, chancroid has been primarily diagnosed in female sex workers and in individuals involved in exchange of sex for illicit drugs.
- b. Chancroid is a known cofactor in HIV transmission, and there is a high incidence of coexisting HIV infection among individuals with chancroid worldwide. Ten percent of patients in the United States with chancroid may also be infected with syphilis or herpes. Testing for HIV should be done on all persons diagnosed with chancroid.

2. **Clinical presentation.** The incubation period from exposure to symptoms is 1 to 35 days. Lesions begin as multiple small pustules in the genital area and progress to 1 to 2 cm painful genital ulcers in 2 to 3 days. If the lesions are left untreated, buboes and inguinal ulcers may develop 1 to 2 weeks after the ulcers appear, accompanied by regional lymphadenopathy. Buboes can spontaneously rupture with pus.

3. **Diagnosis.** Culture is not widely available and is only 80% sensitive. PCR tests are being studied by the CDC and when used at multiple STD clinics across the United States increased diagnosis of chancroid is made. Non-FDA approved PCR testing is available but is still a costly technology and is not widely available in United States. Because of this, the CDC has developed the following criteria for probable diagnosis:

- a. Painful genital ulcers are present without evidence of herpes (culture) or syphilis (darkfield examination and serologic testing). Diagnosis is supported by coexisting painful inguinal adenopathy, which occurs in up to one-third of cases.

4. **Treatment.** Ulcers should start to improve by 3 days posttreatment and resolve by 7 days; larger ulcers may take longer to heal. Lack of response to treatment should cause reconsideration of the diagnosis and also testing for HIV (if not already completed). Witnessed, single dose regimens are generally favored as compliance with treatment is assured. Therapeutic regimens include:

- a. **Azithromycin** 1 g orally (reported cure rate ~90%)
- b. **Ceftriaxone** 250 mg intramuscularly (reported cure rate as high as 98%)
- c. **Ciprofloxacin** 500 mg orally twice daily for 3 days (contraindicated in pregnant women, reported cure rate over 90%)
- d. **Erythromycin base** 500 mg orally three times daily for 7 days, this regimen is effective but limited by prolonged treatment and accompanying nausea

D Granuloma inguinale This genital ulcerative disease, which is also known as donovanosis, is caused by *Klebsiella granulomatis* (also known as *Calymmatobacterium granulomatis*), a Gram-negative intracellular bacterium.

1. **Epidemiology.** This STD is rare in the United States, but it is endemic in some tropical areas including some parts of India, Africa, Brazil and Australia. Ulcers appear after an 8- to 80-day incubation period. Coinfection of ulcers with other STIs may occur.

2. **Clinical presentation.** Affected individuals present with a painless, beefy red, friable ulcerative lesion that develops at the site of inoculation. Infection usually is seen in the genital region but can also occur in the anal, oral or other extragenital sites of inoculation. In genital infections, accompanying inguinal groin swelling is caused by subcutaneous spread of granuloma. This condition may lead to lymphedema and elephantiasis of the external genitalia.

3. **Diagnosis.** Culture of *K. granulomatis* is difficult. When the diagnosis is expected based on appearance of lesions, scrapings of ulcers base and edges can be placed on a glass slide, fixed and stained. Diagnosis is made when pathognomonic cells are seen—mononuclear cells with inclusion cysts containing Gram-negative pleomorphic rod-like organisms, known as Donovan bodies. Biopsy of lesions can also be performed.

4. **Treatment.** Repeat courses of treatment may be necessary. All treatment regimens should be continued until all ulcers have completely healed. Treatment of asymptomatic sex partners is controversial. One of the following therapeutic regimens may be used:

- a. **Doxycycline** 100 mg orally twice daily for at least 3 weeks (and until all lesions have healed) (**Recommended regimen**)
- b. **Trimethoprim–sulfamethoxazole** 160 mg/800 mg orally twice daily for at least 3 weeks (and until all lesions have healed)
- c. **Ciprofloxacin** 750 mg orally twice daily for at least 3 weeks (and until all lesions have healed)
- d. **Erythromycin base** 500 mg orally four times daily for at least 3 weeks (and until all lesions have healed)
- e. Alternative: **Azithromycin** 1 g orally once a week for at least 3 weeks (and until all lesions have healed)

E Lymphogranuloma venereum (LGV) *C. trachomatis*, serotypes L₁, L₂, and L₃, causes LGV, producing a wide variety of local and regional ulcerations and destruction of genital tissues.

1. **Epidemiology.** LGV rarely occurs in the United States and is more frequently seen in tropical countries. It is endemic in heterosexual populations in some parts of Africa, India, Southeast Asia, and the Caribbean. Sporadic outbreaks have been reported in the United States, generally among men having sex with men (MSM). In the MSM population over 2/3 of men diagnosed with LGV are HIV positive.
2. **Clinical presentation.** LGV primarily infects lymphatic tissue. At around 12 days after exposure, primary genital ulcers appear at the site of inoculation. The lesions resolve spontaneously in a few days. Two to six weeks after this, tender, secondary unilateral inguinal or femoral adenopathy develops, which can develop ulceration, abscess formation, and rupture. When the rectum is infected, both men and women experience proctitis with accompanying perianal inflammation and lymphatic involvement, which can lead to tertiary fistula formation and strictures. Genital elephantiasis and infertility can also occur in tertiary disease.
3. **Diagnosis.** Usually, diagnosis is made serologically or by exclusion of other causes of inguinal lymphadenopathy. **A highly accurate PCR assay has recently been developed by the CDC. This test is not yet commercially available.** Complement fixation or microimmunofluorescence are currently the most commonly used methods for diagnosis but do not distinguish between serotypes and do not necessarily distinguish recent from past infection. A twofold rise in titer or a titer of greater than 1/64 is felt to be indicative of active infection when appropriate clinical symptoms are present. Culture is a difficult and therefore unreliable diagnostic tool with low-yield positive results from secondary lymphatic lesions.
4. **Treatment. Prompt treatment eliminates infection and aids in prevention of tissue damage. Delayed treatment will not necessarily reverse tissue damage.**
 - a. Recommended: **Doxycycline** 100 mg orally twice daily for 21 days
 - b. Alternative: **Erythromycin** 500 mg orally 4 times a day for 21 days
 - c. Alternative: **Azithromycin 1 g po weekly for 3 weeks (primary recommendation for treatment in pregnancy but clinical studies of efficacy are lacking)**
 - d. **Surgical reconstruction** may be required for patients with considerable tissue destruction in the tertiary stage. Buboec may need to be incised and drained
 - e. **Sexual partners** of patients diagnosed with LGV should be treated as well. If asymptomatic, partners can be treated with 1 mg azithromax or doxycycline 100 mg bid for 7 days
 - f. **Screening for other STIs, particularly HIV is recommended when LGV is diagnosed**

F Bacterial vaginosis (BV) This vaginal infection results from the replacement of the normal H₂O₂⁻ producing *Lactobacillus* with high concentrations of other bacteria, such as *Gardnerella vaginalis*, *Mobiluncus*, *Bacteroides*, and *Mycoplasma*. BV is included in this chapter, but it is not considered to be an STD. BV is associated with new or multiple sexual partners but is thought to result from alteration in balance in normal flora as opposed to sexual transmission of an infectious agent.

1. **Epidemiology.** BV is the most common cause of vaginal discharge and odor, but 50% of women who meet criteria for diagnosis are asymptomatic. In addition, BV has also become increasingly associated with pregnancy complications, PID, and postprocedure endometritis and cuff cellulitis after hysterectomy.

2. **Diagnosis.** BV may be diagnosed by the use of clinical or Gram-stain evidence. Clinical diagnosis requires three of the following criteria:
 - a. Homogenous, grayish, noninflammatory discharge that adheres to vaginal walls
 - b. Saline preparation of vaginal secretions that reveals squamous cells whose borders are obscured by coccobacillary forms, known as **clue cells**
 - c. **pH** of secretions greater than 4.5
 - d. Fishy odor after addition of **10% potassium hydroxide** (“**whiff**” test)
 - e. Vaginal culture for *G. vaginalis* and Pap smears are not useful because of low sensitivity and specificity
3. **Treatment.** Women with symptomatic disease require treatment. Whether treatment in asymptomatic pregnant women reduces pregnancy-related complications, most notably preterm labor, remains controversial. Studies have shown a reduction in postoperative infections in women who received preoperative treatment. **Effective treatments** include the following:
 - a. **Metronidazole** 500 mg orally twice daily for 7 days
 - b. **Metronidazole gel** (0.75%) one applicator (5 g) intravaginally once daily for 5 days (not recommended in pregnancy)
 - c. **Clindamycin** cream (2%) one applicator (5 g) intravaginally at bedtime for 7 days (not recommended in pregnancy)
 - d. **Alternative regimens: Clindamycin 300 mg orally twice a day for 7 days or Clindamycin ovules 100 mg intravaginally at bedtime for 3 days**

IV

SYPHILIS

The cause of this systemic STD is the spirochete *Treponema pallidum*. It can be transmitted by direct sexual contact with an infected lesion, by contact with the infected blood, or by intrauterine transmission from mother to fetus (congenital syphilis). Syphilis has been called the “great imitator” because of its association with a variety of signs and symptoms.

A Epidemiology With the introduction of penicillin treatment and public health programs in the 1940s, syphilis was nearly eliminated in the United States by 1957. Since then, national epidemics have occurred in a cyclic fashion every 7 to 10 years. Since reporting was initiated in 1941, the lowest rate of primary and secondary syphilis was reported in 2000. Cases have increased recently, with 13,500 new cases of primary and secondary syphilis being reported to the CDC in 2008. Rates were significantly higher in men having sex with men compared with other groups and also were eight times higher in black men and women than white men and women in 2008. In 2008, the rate of congenital syphilis was 10.1 per 100,000 live births, increased compared to 2005. The presence of syphilis increases the risk of acquiring HIV by a factor of two to five.

Screening for syphilis is recommended in pregnant women, commercial sex workers, incarcerated individuals and people diagnosed with another STI, sexually active HIV positive individuals and men having sex with men who engage in high-risk sexual behaviors as well as in individuals with suspicion of infection based on symptoms. Syphilis infection is also associated with increased rates of HIV infection, so HIV testing should also be encouraged in individuals diagnosed with syphilis. When studied, up to 25% of individuals diagnosed with primary syphilis have HIV coinfection.

B Clinical presentation

1. Infection is transmitted through direct contact with an infected lesion (chancre, condyloma latum) during sexual activity with an approximate 30% risk of transmission with a single contact. The **initial lesion** of primary syphilis is initially a papule which evolves into a painless, ulcerated, hard **chancre**, usually on the external genitalia, although vaginal cervical, pharynx, and anus lesions may also be detected. Incubation time from exposure to first symptom is 3 to 90 days with a median time of 21 days. The primary lesions resolve in 2 to 6 weeks. These lesions are teeming with spirochetes and are infectious.
2. In about 25% of **untreated patients**, this chancre is followed in 6 weeks to 6 months by a **secondary or bacteremic stage** in which the skin and mucous membranes are affected. A diffuse **maculopapular rash** of the palms, soles, and mucous membranes occurs. Warm moist areas may

develop **Condyloma latum** (large, pale grey to white lesions) and **generalized lymphadenopathy** can be seen as well. Systemic symptoms of fever and malaise may also be present. The liver, gastrointestinal tract, kidneys, musculoskeletal system, eyes, and nervous system can also be affected.

3. Approximately 33% of untreated patients progress to late or **tertiary syphilis** with **multiple organ involvement**. This can occur as early as 1 year but up to 25 years after initial infection. Endarteritis leads to aortic aneurysm and aortic insufficiency, other long consequences of tertiary syphilis are tabes dorsalis, optic atrophy, and meningovascular syphilis, as well as uncreative or granulomatous gummatous lesions of bone, cutaneous and subcutaneous tissues.
4. **Latent infection** occurs in infected individuals with no clinical manifestations of the disease. Latent infection is detected serologically and classified as **early latent** (infection of less than 1 year's duration) or **late latent** (infection of more than 1 year's duration) or latent syphilis of unknown duration. Longer treatment duration is generally recommended for individuals with late latent syphilis.
5. Identification and treatment of pregnant women with diagnosed syphilis is the mainstay of prevention of **congenital syphilis**. Untreated congenital syphilis may cause stillbirth, nonimmune hydrops, jaundice, infant hepatosplenomegaly, and skin rash and pseudoparalysis of an arm or leg.

C Diagnosis Since culture of *T. pallidum* is not possible, other diagnostic methods are utilized.

1. **Darkfield examination** of fresh specimens from chancres (primary) and blood (secondary) detects spirochetes in the primary and secondary stages of the disease. Direct fluorescent antibody testing and PCR testing can also be done directly on clinical specimens. These procedures rely on fresh specimens and are labor intensive and are therefore not the primary method for diagnosis. **Serologic tests** are useful in diagnosing syphilis in patients who have progressed beyond primary disease. In the primary stage, infected individuals have not had sufficient time to mount an immune response that can be serologically detected. There are **two types of serologic tests**.
2. **Nontreponemal tests** are measured quantitatively in titers and usually correlate with disease activity. These tests rely on nonspecific (though sensitive) antibody to antigen reaction. They are generally used for initial screening. These tests may become negative after treatment, but a low-level positive titer can persist for many years. A fourfold increase or decrease in titer using the same test is believed to be clinically significant. False-positive results are associated with pregnancy, several other infections and autoimmune diseases. Since testing relies on humoral immune response, false-negative testing may occur in individuals with active HIV infection. Conversely, underlying HIV disease has also been reported to be associated with false-positive nontreponemal testing. The two commonly utilized nontreponemal tests are:
 - a. Rapid plasma reagin (RPR)
 - b. Venereal Disease Research Laboratory (VDRL)

Because they are nonspecific, a positive nontreponemal test must be confirmed by a more specific treponemal test.
3. **Treponemal antibody tests**. Since these tests are more difficult to perform they are reserved for the confirmation of syphilis diagnosis after a positive nontreponemal test. They rely on detection of antibodies to treponemal specific antigens. Recently, automation has made these tests easier to perform. Early treatment of primary syphilis makes it more likely that treponemal antibody tests will become negative but treponemal tests can remain positive for years in adequately treated patients. Treponemal antibody titers are not used to assess treatment response because they correlate poorly with disease activity and tests are generally reported as simply positive (reactive) or negative (nonreactive). There are four treponemal antibody tests:
 - a. Fluorescent treponemal antibody absorption (FTA-ABS)
 - b. *T. pallidum* particle agglutination (TP-PA)
 - c. Microhemagglutination test for antibodies to treponema pallidum (MHA-TP)
 - d. Treponema pallidum enzyme immunoassay (TP-EIA)
4. Both types of serologic tests should be used to diagnose syphilis because various medical conditions can cause false-positive RPR or VDRL. When treponemal antibody testing confirms true infection, serial nontreponemal test titers are utilized to guide management.

5. When lesions suspicious for chancre are present, microscopic darkfield examination for spirochetes may be more helpful for diagnosis since 20% to 30% of people presenting with chancre have nonreactive nontreponemal testing.
6. The diagnosis of **neurosyphilis** is made by performing a VDRL test on cerebrospinal fluid (CSF). While a positive CSF test is diagnostic of neurosyphilis, only 50% of individuals with neurosyphilis test positive.

D Treatment

1. General considerations

- a. **Need for treatment.** Individuals with a history of sexual contact with a person with documented syphilis, a positive darkfield examination, or serologic testing with positive nontreponemal and antitreponemal testing should be treated. Sexual contacts of patients receiving therapy should also be treated. Possible reinfection should also prompt treatment; a fourfold increase in a quantitative antitreponemal titer implies reinfection.
- b. **Safety of therapeutic regimens.** Treatment regimens are based on duration and severity of syphilis. Alternative treatments are listed for penicillin-allergic patients, but much less objective evidence exists for optimum dosing and duration of these alternative regimens. The **Jarisch–Herxheimer reaction**, an acute febrile reaction that may be accompanied by myalgias, headache, and other systemic symptoms, can occur within 24 hours after treatment of syphilis at any stage, especially early disease.

2. Specific regimens

- a. **Early disease:** primary, secondary, and asymptomatic recent sexual contacts:
 - (1) **Benzathine penicillin G** 2.4 million units intramuscularly in a single dose
 - (2) **Doxycycline** 100 mg orally twice daily or **tetracycline** 500 mg orally four times daily for 2 weeks in nonpregnant patients with penicillin allergy
- b. **Latent syphilis:** treatment of latent syphilis is performed to prevent late syphilis complications. Because treatment for neurosyphilis is different, it is recommended that CSF evaluation be considered in patients diagnosed with latent syphilis. Recommended regimens for nonpenicillin allergic latent syphilis patients with normal CSF examination is:
 - (1) **Early latent syphilis: benzathine penicillin G 2.4 million units intramuscularly in a single dose**
 - (2) **Latent or unknown duration syphilis: benzathine penicillin G** 2.4 million units intramuscularly every week for 3 weeks
 - (3) **Doxycycline** 100 mg orally twice daily or **tetracycline** 500 mg orally four times daily for 4 weeks in nonpregnant patients with penicillin allergy
- c. **Neurosyphilis**
 - (1) This form of syphilis may occur at any stage of infection with *T. pallidum*. It should be suspected in patients who are HIV positive, fail initial treatment, have an initial titer in excess of 1:32, have neurologic or ophthalmic signs or symptoms, or are diagnosed with aortitis or gummas. Diagnosis is made by testing the CSF.
 - (2) Recommended treatment is aqueous crystalline **penicillin G** 18 to 24 million units per day, given 3 to 4 million units intravenously every 3 to 4 hours or by continuous infusion for 10 to 14 days. Alternatively, **procaine penicillin** 2.4 million units can be given IM once daily with **probenecid** 500 mg orally four times daily, both for 10 to 14 days. For penicillin-allergic patients, **ceftriaxone** 2 g/d, either intramuscularly or intravenously, for 10 to 14 days may be used. The use of ceftriaxone in penicillin-allergic patients is limited by the possibility of cross-allergy to cephalosporins. However, other treatment regimens have not been tested adequately for patients with neurosyphilis.
- d. **Penicillin-allergic pregnant patients.** These patients should undergo **skin testing** followed by **penicillin desensitization** for two reasons: tetracycline and doxycycline are contraindicated in pregnancy, and only penicillin has been proven to prevent fetal infection.
- e. **Congenital syphilis**
 - (1) Treatment is recommended for infants who are strongly suspected of being born with syphilis because of specific abnormalities on physical examination, serum nontreponemal serologic titer four times greater than the maternal titer, positive darkfield examination of infant body fluid, or history of inadequately treated maternal syphilis.

- (2) The recommended regimen is aqueous crystalline **penicillin G** 100,000 to 150,000 units/kg/d, administered in divided doses of 50,000 units/kg intravenously every 12 hours for the first 7 days of life and every 8 hours after this for a total of 10 days. Alternatively, **procaine penicillin G** 50,000 units/kg/dose, intramuscularly once daily, can be given for the first 10 days of life. In addition, benzathine penicillin 50,000 units/kg/dose can be given as a single IM dose.

E Follow-up

1. Patients should be tested by VDRL or RPR at 3, 6, and 12 months. Patients with early syphilis should have a fourfold decline in titer by 3 months posttreatment. Retreatment should be considered for a fourfold increase in titer, for failure of an initial titer greater than 1:32 to decrease fourfold 12 to 14 months after treatment, or if symptoms or signs of disease occur after treatment. Close serologic follow-up is warranted in patients treated with alternative regimens.
2. All patients diagnosed with syphilis should be tested for HIV. When neurosyphilis has been diagnosed and treated, follow-up CSF examination should be performed every 6 months until the cell count is normal.

V

VIRAL SEXUALLY TRANSMITTED DISEASES

A HIV Originally identified in 1981, this unique retrovirus is believed to be responsible for severe deficiencies in cell-mediated immunity, leading to unusual opportunistic infections, malignancy, and, eventually, death. The disease caused by HIV is known as **AIDS**. If left untreated, AIDS develops in almost all HIV-infected individuals; 87% develop AIDS within 17 years of HIV infection.

1. **Epidemiology.** As of December 2009, 33 million individuals were estimated to be infected with HIV worldwide and more than half of infected people are women. A total of 2.7 million of these were newly diagnosed infections in 2008 and 1.2 million people were living with HIV/AIDS in 2008. Two-thirds of the infected population reside in sub-Saharan Africa. Globally, sub-Saharan African and Caribbean countries currently have the highest rates of HIV infection.
 - a. Exhaustive epidemiologic studies have demonstrated that male homosexuals and bisexuals, intravenous drug users, female heterosexual consorts of infected men, recipients of tainted blood or concentrated blood products, and neonates born to infected women are the predominant populations at risk. In addition, African Americans and Hispanics are more likely than Caucasians to become infected with HIV. Recent studies show that currently more than 80% of infections are transmitted through sexual contact. The CDC now recommends routine screening for HIV in all sexually active individuals and HIV screening is part of routine prenatal care.
 - b. Transmission is both horizontal and vertical. **Incubation or latency time** is between 2 months and 17 years.
 - c. Other STDs increase susceptibility to HIV infection in two ways.
 - (1) Genital ulcers cause breaks in the mucosa and skin in areas exposed to HIV through sexual contact, facilitating entry of HIV.
 - (2) Nonulcerative STDs, such as chlamydia and gonorrhea, increase the local concentration of immune system-mediated HIV target cells, such as CD4+ cells. In addition, when HIV-infected individuals have other STDs, HIV is more likely to be present in their genital secretions. These observations support the value of HIV testing whenever another STD is diagnosed, as well as contact tracing and treatment of sexual partners if STDs are diagnosed.
 - d. Most HIV infections in the United States are caused by HIV type 1 (HIV-1). However, rare cases of HIV type 2 (HIV-2) have been documented in the United States. Epidemiologic risk factors for HIV-2 are a sex partner from western Africa, where HIV-2 is endemic, or a history of nonsterile injection or blood transfusion in West Africa.
2. **Clinical presentation.** Approximately 80% to 90% of infected individuals are asymptomatic carriers.
 - a. **Initial exposure to HIV** results in a retroviral syndrome in about 70% of patients.

- (1) **The usual incubation period is 2 to 4 weeks.**
 - (2) **Symptoms** include **febrile** pharyngitis, fever, sweats, myalgias, arthralgia, headache, and photophobia.
 - (3) **Lymphadenopathy** is **usually** generalized and begins in the second week.
 - b. Later, a more severe form of the disease may occur.
 - (1) **Symptoms** are generalized lymphadenopathy, night sweats, fever, diarrhea, weight loss, and fatigue.
 - (2) Infections such as **herpes zoster virus** and **oral candidiasis** may occur.
 - (3) **If untreated**, within 4 to 5 years, 30% of cases of HIV infection progress to AIDS.
 - c. **AIDS is the final stage in HIV infection**
 - (1) It is manifested by **severe alterations of cell-mediated immunity** (reversal of the CD4 [helper T cell]-to-CD8 [suppressor T cell] ratio).
 - (2) Lymphadenopathy, Kaposi sarcoma, opportunistic infections, malaise, diarrhea, weight loss, and death result.
3. **Diagnosis**
- a. Serologic screening with **enzyme-linked immunosorbent assay (ELISA)** for individuals at risk detects more than 95% of patients within 3 months of infection.
 - b. A positive ELISA is confirmed by a repeat ELISA and then a **Western blot analysis**, which is more specific.
 - c. Many states require pretest and posttest counseling and written informed consent for HIV testing. The CDC is currently recommending routine testing of all sexually active people.
 - d. If acute retroviral syndrome is suspected, viral load testing for HIV plasma RNA should be performed. If HIV is detected, another test should be performed for confirmation purposes. Current research suggests that early treatment at this time may be beneficial.
4. **Treatment.** Care of HIV-positive patients involves:
- a. A thorough history and physical examination, including gynecologic examination and Pap smear
 - b. Evaluation for associated diseases, such as STDs including hepatitis B and C and tuberculosis (TB)
 - c. Identification of patients in need of immediate medical care and antiretroviral therapy or prophylaxis for opportunistic infections
 - d. Determination of need for referral
 - e. Administration of recommended vaccines
 - (1) Pneumococcal
 - (2) Influenza
 - (3) Hepatitis B if susceptible
 - (4) Measles if needed
 - (5) *Haemophilus influenzae* B
 - f. Psychosocial and behavioral evaluation and counseling, including counseling about high-risk behaviors as well as identification of sexual partners for testing
 - g. Complete blood count and CD4+ T-lymphocyte count. The **CD4+ T count** is the best laboratory indicator of clinical progression, and management strategies are stratified by CD4+ count
 - h. The **purified protein derivative test** and **anergy panel** should be administered to all HIV-positive patients
 - (1) HIV may cause cutaneous anergy.
 - (2) An area of induration larger than 5 mm in HIV-positive patients is considered indicative of TB infection. Preventive therapy with isoniazid should be considered after excluding active TB.
 - i. **Additional studies** may include chest radiograph, serum chemistry, antibody testing for toxoplasmosis and hepatitis B and C, and RPR.
 - j. **Antiretroviral therapy** may delay progression to advanced disease. Several antiretroviral agents are used for highly active antiretroviral therapy (HAART). Referral for treatment should be considered for asymptomatic patients with CD4+ less than 500/mm³ and for all symptomatic patients. The goal of therapy is suppression of HIV-1 RNA below detectable levels. Selection of antiretroviral therapy agents is beyond the scope of this chapter.

k. ***Pneumocystis carinii* pneumonia (PCP) prophylaxis** with one of the following agents should be given to patients with CD4+ counts less than 200/mm³ or with constitutional symptoms or previous PCP infection:

- (1) **Trimethoprim–sulfamethoxazole** one double-strength tablet orally daily
- (2) **Aerosolized pentamidine** 300 mg once a month make sure all this current

l. Nutritional evaluation and counseling

5. **Pregnancy.** HIV testing should be offered to all pregnant women, and those individuals who are HIV positive should be evaluated as previously described. Without treatment, the risk of transmission to the fetus is 15% to 25%. Breastfeeding increases transmission by an additional 12% to 14%. Neonatal transmission can be decreased to less than 2% with maternal treatment, cesarean delivery for women with detectable viral load, and avoidance of breastfeeding for all women diagnosed with HIV.

B HPV The genital virus in this double-stranded DNA family is responsible for a variety of mucocutaneous genital lesions, affecting both men and women. It is also known to be associated with lower genital tract cancers, especially cervical intraepithelial neoplasia (CIN).

1. **Epidemiology.** More than 20 million people in the United States are infected with HPV making it the most common viral sexually transmitted disease. Between 50% and 75% of sexually active men and women acquire HPV at some time in their lives. Risk of HPV infection increases with number of sexual partners and diagnosis of any other sexually transmitted disease. Viral expression, symptoms, persistence and oncogenicity on both viral type and the immune response of an infected individual.

a. The **predominant means of transmission** is through **sexual contact**. In women whose sexual partners have obvious genital warts, the risk of contracting warts is 60% to 85%. Incubation time is between 6 weeks and 18 months, with a mean of 3 months. Most infections clear within 2 years.

b. **Transmission to the fetus may occur**, occasionally causing neonatal and juvenile respiratory papillomatosis. However, the risk is low, occurring in 1 of 1,000 fetuses of infected mothers. Potential routes include transplacental, intrapartum, or postnatal. Since the risk of transmission is low and no controlled study has shown that cesarean section prevents neonatal infection, the presence of HPV infection is not an indication for cesarean section.

c. **Genital** warts can sometimes grow extensively during pregnancy and may need removal because of their size and friability. Also, cesarean section may be necessary if wart proliferation obstructs the vagina or makes the vaginal surface extremely friable. Exuberant exacerbation of genital warts during pregnancy generally regresses without treatment after delivery.

d. More than 35 types of HPV have been found in genital tract infections. Multiple types can infect an individual person.

(1) HPV types 6 and 11 are the usual causes of visible external warts.

(2) HPV types 16, 18, 31, 33, 35, 45, and 59 have all been associated with CIN and/or with external genital squamous intraepithelial neoplasia. Types 16 and 18 are the most commonly associated with cervical or anal squamous cell carcinoma.

2. **Clinical presentation.** Genital HPV infections are frequently asymptomatic. Lesions include overt anogenital warts (condyloma acuminatum) and dysplastic lesions. Lesions can also be subclinical or latent (not visible to the naked eye). Visual inspection of overt warty disease of the lower genital tract detects obvious lesions, which are often multifocal in distribution.

3. **Diagnosis**

a. **Direct inspection** discerns overt warts. Their nature can be confirmed by biopsy if any doubt exists.

b. Approximately 2% to 4% of **Pap smears** demonstrate the pathognomonic cell—the koilocyte (or halo cell). This exfoliated squamous cell has a wrinkled, somewhat pyknotic nucleus surrounded by a perinuclear clear zone or halo. Pap smears with this change are designated as low-grade squamous intraepithelial lesions.

c. **Colposcopy**, the magnified inspection of lower genital tissues after staining with a weak acetic acid solution, is helpful in detecting latent or associated precancerous lesions caused by HPV. The lesions are flat, small, and acetowhite, with vascular punctuation or mosaicism. Histologically, these lesions reveal koilocytosis, acanthosis, and variable nuclear atypia.

- d. **DNA hybridization techniques** have been used not only to detect HPV, but also to ascertain viral type. Viral typing is becoming an increasingly useful tool in the evaluation of Pap smears with atypical squamous cells of undetermined significance (ASCUS). In addition, testing for high-risk HPV types is a component of strategies in women older than 30 years at low risk of developing cervical cancer to aid in selection of patients who can safely lengthen cervical cancer screening interval. Research is ongoing in continuing definition of a role for cervical high-risk HPV testing as a component of cervical cancer screening.
4. **Treatment of anogenital external warts:** Even without treatment, many warts resolve. Therapy does not necessarily eradicate the virus. Treatment of visible warts is aimed at providing symptomatic relief and may reduce, but does not entirely eliminate, the ability of an infected individual to transmit HPV through sexual contact.
 - a. **Patient-applied methods**
 - (1) Podophylotoxin solution or gel causes arrest of mitosis by binding to microtubules. Patients apply this medication to warts twice daily for 3 days followed by 4 days off for up to four cycles. Up to 94% of genital warts have been shown to be eradicated with application of podophylotoxin.
 - (2) Imiquimod cream is an immune response modifier. Patients apply this medication to warts three times a week at bedtime and wash it off after 6 to 10 hours. This cream can be used for up to 16 weeks and produces a 72% to 84% clearance rate with a 5% to 19% recurrence rate. Imiquimod cannot be used internally and is not recommended for use in pregnancy.
 - b. **Provider-applied methods**
 - (1) Cryotherapy with liquid nitrogen or a cryoprobe produces a 63% to 72% clearance rate.
 - (2) Podophylic resin 10% to 25% applied once or twice weekly (antimitotic therapy)—less effective than podophylotoxin therapy (should not be used internally or during pregnancy)
 - (3) Bichloro- or trichloroacetic acid 80% to 90% can be used on external genital and vaginal and cervical lesions as well as during pregnancy. It works by causing local destruction of warts via protein coagulation. Care must be used in application to avoid damage to surrounding normal tissue since this agent is very caustic. Petroleum jelly can be applied to protect surrounding tissue during treatment.
 - (4) Surgical excision or ablation with cautery or laser produces high clearance rates but recurrence of up to 45% has been observed after treatment. 5-Fluorouracil epinephrine gel causes lesion destruction by blocking the methylation in DNA synthesis. It is injected into lesions with a high effectiveness rate after multiple injections. However, recurrence rate after treatment is 50% to 60%.
 - c. **Methods for treatment of HPV-related precancerous conditions in the cervix.** Pap smear screening and colposcopic diagnoses are the mainstay of determining extent and severity of HPV-triggered cervical lesions. Low grade lesions resolve spontaneously in the majority of cases. Treatment of cervical disease is reserved for high grade and persistent low grade change. Treatment methods rely on removal or destruction of lesions defined on colposcopy as well as the cervical transformation zone. Methods for excision/destruction for treatment of cervical dysplasia include:
 - (1) Loop electrode excision of the transformation zone
 - (2) Laser vaporization
 - (3) Cryotherapy
 - (4) Cone biopsy of the cervix
 - d. The treatment of **latent HPV cervical infections** without dysplasia is not recommended.
 - e. Vaccination against several strains of HPV was introduced in the United States in 2006 and is recommended for both boys and girls aged 9 to 26 years. There are currently two vaccines available in the United States. Gardasil (Merck) was approved in 2006. This quadrivalent vaccine immunizes against type 6, 11, 16, and 18. Initially approved for use in girls aged 9 to 26 years. Gardasil has been more recently approved by the FDA for immunization of boys and young men as well. More recently, another bivalent vaccine, Cervarix (Glaxo-Smith Kline) was approved for use in females aged 10 to 25 years. Cervarix immunizes against viral types 16 and 18. Immunization is intended to decrease infection and subsequent development of cervical intraepithelial neoplasia.

C Herpes simplex virus (HSV) HSV-2, a double-stranded DNA virus, is the predominant genital pathogen, although HSV-1 is seen in approximately 13% to 15% of herpetic genital infections. Both these viruses have an affinity for **infecting mucocutaneous tissues of the lower genital tract** and are maintained in pelvic ganglia as a latent reservoir for recurrent herpetic genital infection. Patients with active HSV infection are at increased risk for acquiring HIV when exposed.

1. **Epidemiology.** Seroprevalence studies in the United States showed that 17% of 14- to 49-year-olds tested positive for antibody to type 2 HSV. Over 50% of affected Americans are unaware that they have HSV. The predominant mode of transmission is sexual intercourse. HSV is responsible for the highly lethal neonatal meningitis in infants delivered through an actively infected lower genital tract. The **incubation time from exposure to symptoms for genital herpes** is between 3 and 7 days. Frequency of recurrence is influenced by severity and duration of the primary episode as well the serotype of the infection virus and the host immune response.
2. **Clinical presentation.** The most common signs of HSV are recurrent vesico-ulcerative genital lesions. Primary genital herpetic infections may also be accompanied by systemic viral symptoms such as fever, myalgias, headache, and general malaise. Vulvar paresthesia may precede the development of genital vesicular lesions. Asymptomatic viral shedding can also occur.
 - a. **Primary lesions start as small vesicles and then** become shallow, coalescent, painful ulcers in a few days and may last for 2 to 3 weeks. These lesions may be accompanied by severe dysuria with urinary retention, mucopurulent vaginal discharge, painful inguinal adenopathy, generalized myalgias, headaches, and fever.
 - b. **Recurrent lesions** are similar but less severe in intensity, duration, and systemic side effects. **Menses** and **stressful life situations** are associated with recurrent outbreaks. Up to 89% of patients have recurrent symptoms. Recurrence is more likely with HSV-2 than HSV-1 infection.
 - c. Infants who come into contact with maternal active infection at birth are at risk for potentially fatal systemic infections. This situation is most likely to occur in infants born to mothers who are having their initial outbreak. When maternal active herpes infection is suspected at term or at the time of labor, cesarean section is generally the recommended route for delivery.
3. **Diagnosis. Herpes cultures** obtained from the vesicular fluid or the edge of the ulcerative lesion give the best results. Cultures are also most likely to be positive early in the outbreak. **Cytologic demonstration** of multinucleated epithelial cells with intranuclear inclusions is helpful in the diagnosis. Newer PCR testing has recently been introduced and is thought to be more sensitive than culture but use is limited secondary to cost of testing. When the diagnosis is uncertain, testing for type-specific antibody to HSV-1 or -2 can be performed.
4. **Treatment**
 - a. **Primary herpes.** Initiation of one of the following regimens as soon as diagnosis is suspected is appropriate to decrease severity and duration of primary infection:
 - (1) **Acyclovir** 400 mg orally three times daily for 7 to 10 days or 200 mg orally five times daily for 7 to 10 days
 - (2) **Famciclovir** 250 mg orally three times daily for 7 to 10 days
 - (3) **Valacyclovir** 1 g orally twice daily for 7 to 10 days
 - b. **Recurrent herpes.** Prompt treatment with one of the regimens below decreases duration and severity of symptoms. Initiation of treatment should be done as soon as possible since treatment is more effective when initiated within 24 hours of symptom occurrence.
 - (1) **Acyclovir** 400 mg orally three times daily for 5 days or 800 mg orally two times daily for 5 days or 800 mg orally three times a day for 2 days
 - (2) **Famciclovir** 125 mg orally twice daily for 5 days or 1,000 mg orally twice a day for 1 day
 - (3) **Valacyclovir** 1 g orally once daily for 5 days or 500 mg orally twice a day for 3 days
 - c. Suppressive therapy is used to reduce recurrences by 70% to 80%. Suppressive therapy can be utilized by patients who either have frequent and/or severe recurrence. Asymptomatic shedding and infection of noninfected sexual partners may also be decreased by continuous regimens. Because risk of recurrence varies over time even without suppressive treatment, suppressive treatment should be periodically reevaluated. The benefits and risks of suppressive therapy for longer than 6 years have not yet been studied. Condom use to decrease transmission should also be encouraged in discordant couples. One of the following regimens is appropriate for suppressive treatment:

- (1) **Acyclovir** 400 mg orally twice daily
- (2) **Famciclovir** 250 mg orally twice daily
- (3) **Valacyclovir** 500 mg orally once daily or 1.0 g orally once a day (500 mg dose may be less effective than other regimens in patients with 10 or more recurrences a year)

D Molluscum contagiosum

1. **Epidemiology.** Molluscum contagiosum is mildly contagious and is caused by a double-stranded DNA poxvirus. The incubation period is several weeks.
2. **Clinical presentation.** This virus creates small (1 to 5 mm), umbilicated papules in the cutaneous genital region of sexually active individuals. It may also affect the nongenital skin.
3. **Diagnosis.** The lesion itself is pathognomonic, but the diagnosis can be confirmed on histologic demonstration of a papule with a hyperkeratotic plug arising from an acanthotic epidermis. There are intracytoplasmic molluscum bodies noted on Wright stain.
4. **Treatment.** The disease is usually self-limited, with spontaneous resolution in 6 to 9 months. Local excision, cryotherapy, electrocautery, and laser vaporization are suitable treatment modalities to decrease the duration of symptoms.

E Hepatitis B virus (HBV)

1. **Epidemiology.** There were approximately 60,000 new infections in the United States in 2004, check stats down from an average of 260,000 in the 1980s. However, approximately 1.25 million chronically infected individuals serve as a reservoir. In the United States, HBV is most commonly transmitted sexually. The disease can also be transmitted by exposure to infected blood. The incubation period is 6 weeks to 6 months. Fifteen to twenty-five percent of those with chronic infection die of liver disease.
2. **Clinical presentation.** HBV infection is symptomatic in adults in about 50% of cases. When symptoms are present, they include jaundice and general malaise. Only 2% to 6% of infected adults become chronically infected, but 90% of congenitally infected infants develop chronic infection.
3. **Diagnosis.** Presence of hepatitis B surface antigen (HBsAg) indicates either acute or chronic infection. Presence of hepatitis B surface antibody (anti-HBs) is indicative of immunity, either through prior infection or immunization.
4. **Treatment and prevention.** Supportive treatment is used for acute HBV infection, which is self-limited. Interferon-alfa and lamivudine have been used in attempts to treat chronic hepatitis B. Vaccination is the mainstay of prevention. Hepatitis B immune globulin (HBIG) provides postexposure prophylaxis, and the multidose hepatitis B vaccine gives longstanding immunity.
5. **Pregnancy.** All pregnant women are tested for HBsAg carrier status. When a pregnant woman is identified as a chronic carrier, fetal infection can be prevented by prompt infant immunization and HBIG administration.

F Hepatitis C virus (HCV)

1. **Epidemiology.** Hepatitis C infection is the most common blood-borne infection in the United States and evidence of hepatitis C infection has been found in approximately 2% of the adult population of the United States. The main mode of transmission is through exposure to infected blood products or contaminated needles. While sexual contact with IV drug abusers and sexual contact with multiple partners has been associated with an increased risk of hepatitis C infection it is not clear whether this is because HCV is sexually transmitted or because high-risk sexual activity is associated with unacknowledged drug abuse.
2. **Clinical presentation.** Most patients are asymptomatic. When symptoms occur they are vague and nonspecific such as malaise, nausea, fatigue, myalgias and generalized weakness. Chronic HCV infection can lead to cirrhosis (10% to 20%) and subsequent chronic liver disease complications including hepatocellular carcinoma.
3. **Diagnosis.** Initial testing is generally done with enzyme-linked immunosorbent assay for HCV antibody and followed with confirmatory recombinant immunoblot assay and HCV RNA polymerase chain reaction. Screening is currently recommended only for persons with risk factors for HCV and not for the general population. When liver disease is diagnosed, testing for HCV infection is also appropriate.

4. **Treatment and prevention.** Interferon and ribavirin are current standard therapies for HCV infection. The goal of treatment is to prevent cirrhosis and subsequent sequelae of chronic liver disease. Since there is currently no vaccine for HCV, screening of donor blood prior to transfusion and avoidance of high-risk behaviors such as needle sharing are the mainstays of prevention.

VI

TRICHOMONIASIS

Of all sexually transmitted protozoal infections, *Trichomonas vaginalis* infection is the most common. While infection can be asymptomatic, trichomoniasis can cause **acute vulvovaginitis in women and urethritis in men.**

A Epidemiology Approximately 5 million infections are caused by *T. vaginalis* annually in the United States. Trichomonas is diagnosed in up to 35% of women presenting with vulvovaginitis complaints. Transmission of this STD is usually by sexual intercourse. Coinfection with other STIs is frequently seen in women diagnosed with trichomoniasis.

B Clinical presentation

1. Profuse, yellow-green, malodorous, frothy discharge of low viscosity
2. Vulvar pruritus
3. Vaginal erythema and occasional intense erythematous mottling of the cervix (**strawberry cervix**)
4. Usually asymptomatic male partner
5. Appearance of symptoms usually 5 to 28 days after exposure
6. Infected men are usually asymptomatic but may have nongonococcal urethritis
7. In both sexes carriers may be asymptomatic for long periods of time

C Diagnosis

1. Vaginal pH between 5 and 6
2. Inflammatory response and motile, flagellated trichomonads on wet mount preparations, best appreciated when wet mount is promptly viewed. Diagnosis on wet mount has a 60% to 70% sensitivity when compared to culture
3. Cultures for *Trichomonas* are available but are usually reserved for resistant cases in which antimicrobial testing can be used
4. Newer immunochromatic and nucleic probe tests with 83% sensitivity and 97% specificity are available. Positive results on these tests should be interpreted with caution in low prevalence populations

D Treatment Therapy using metronidazole in either of the following regimens produces cure rates of greater than 95%. Patients should be counseled to avoid alcohol during treatment with metronidazole and tinidazole because of a possible Antabuse reaction. Sexual partners must be treated to prevent reinfection.

1. **Metronidazole** or **tinidazole** 2 g orally single dose
2. **Metronidazole** 500 mg orally twice daily for 7 days

VII

ECTOPARASITES

This group of STDs includes pediculosis pubis and scabies.

A Pediculosis pubis (*Phthirus pubis*) The **crab louse** is a slow-moving insect approximately 1 mm long. It lays its eggs (**nits**) at the base of hair follicles. After 7 days, nymphs arise from the nits and progress to the adult stage in 2 to 3 weeks. Adult life expectancy of the pubic louse is 30 days.

1. **Epidemiology.** Pediculosis pubis is **highly contagious**. The crab louse can be transmitted through direct sexual contact or **through** fomites, such as blankets and sheets. Hard, smooth surfaces such as toilet seats are not suitable fomites for the transmission of the crab louse.

2. **Clinical presentation.** Intense vulvar pruritus secondary to an allergic sensitization is the presenting symptom.
3. **Diagnosis.** Identification of the crab louse or nits can be made with a **hand lens inspection** of the hair-bearing pubic region.
4. **Treatment.** The specific treatments listed are not recommended for use in the eye area. When eyelashes are infected, treatment **involves** application of an occlusive ophthalmic ointment to eyelids two times daily for 10 days. Resistance to treatment a and b below is widespread and retreatment with different agents may be necessary.
 - a. **Permethrin** cream, 1%, rinse applied to affected areas and rinsed after 10 minutes.
 - b. **Pyrethrins with piperonyl butoxide** applied to the affected area and washed off after 10 minutes.
 - c. **Malathion 0.5%** lotion applied and washed off after 8 to 12 hours. Duration of treatment and odor of medication limits use to treatment failures with the above.
 - d. **Ivermectin** 250 mg/kg, repeated in 2 weeks.
 - e. **Lindane** solution, 1%, applied to infested area for 4 minutes and then washed off. Lindane is contraindicated in pregnancy and lactation and in children less than 2 years of age. Lindane is not recommended for first-line therapy since toxicity includes seizures and aplastic anemia and has been reported when exposure exceeded 4 minutes. Use of lindane should be limited to a 4-minute exposure in nonpregnant or lactating adults weighing more than 100 lb and should be reserved for treatment failures with other medications.
 - f. **Cleaning of all contaminated bedding and clothing** is essential. Decontamination by machine washing and heat drying or dry cleaning is warranted.
5. **Follow-up.** Infected individuals should be re-evaluated 1 week after treatment for nits or lice. Retreatment with an alternative regimen is indicated for persistent infestation. All sexual partners within the past month should be treated. Infected patients should be evaluated for other STIs.

B Scabies (*Sarcoptes scabiei*) This mite is 0.4 mm in length. Unlike the crab louse, it can be found anywhere on the skin, where it burrows a 5-mm-long tunnel to lay its eggs. Its life span is approximately 30 days.

1. **Epidemiology.** Scabies can be transmitted by close sexual contact but also by nonsexual contact, such as sharing clothing or bedding.
2. **Clinical presentation.** The predominant symptom is severe, intermittent itching. Hands, wrists, breasts, and buttocks are the most commonly affected sites. With initial infection, sensitization to scabies must occur before pruritus begins. Therefore, it can take several weeks after exposure for symptoms to develop with initial infections. Intense itching can occur within 24 hours of exposure in subsequent infections.
3. **Diagnosis.** Linear burrows are frequently seen with a hand lens. Microscopic slides prepared from scrapings of suspected lesions in mineral oil often demonstrate adult mites, eggs, and fecal pellets.
4. **Treatment**
 - a. **Permethrin** cream, 5%, applied to the body from the neck down and washed off after 8 to 14 hours.
 - b. **Ivermectin** 200 mg/kg, given orally and repeated in 2 weeks.
 - c. **Lindane** solution, 1%, applied from the neck down and washed off after 8 hours (should not be applied after a bath, when extensive dermatitis is present, in pregnancy or lactation, and in children younger than 2 years of age [see VI A 4 e]). Lindane resistance has been reported in some areas of the world, including the United States. Potential for toxicity (see treatment for pediculosis pubis) also limits its use.
 - d. As with pubic lice, **cleaning of all contaminated bedding and clothing** is essential. Decontamination by machine washing and heat drying or dry cleaning is warranted. All close personal or household contacts within the preceding month should be examined and treated.
5. **Follow-up.** The rash and itching associated with scabies can persist for up to 14 days after treatment. If symptoms persist after 2 weeks, reinfection could be present and retreatment should be considered, especially if live mites are observed. Sexual partners and close personal contacts should also be examined and considered for treatment.



Study Questions for Chapter 33

Directions: Match each description below with the causative agent. Each answer may be used once, more than once, or not at all.

QUESTIONS 1–8

- ☐ A *H. ducreyi*
- ☐ B Genital herpes
- ☐ C *Chlamydia trachomatis* serotypes L 1 to 3
- ☐ D Chancre
- ☐ E HPV
- ☐ F Hepatitis B
- ☐ G HIV
- ☐ H Pediculosis pubis

1. Painless ulcer appearing 3 to 90 days after exposure
2. Presenting with painful genital ulcer, more commonly seen in sub-Saharan Africa
3. Prompt treatment necessary to prevent cutaneous tissue damage
4. Neonatal infection in susceptible babies preventable by effective maternal treatment and avoidance of breastfeeding
5. Treatable with permethrin
6. Neonatal infection in susceptible babies preventable by neonatal IGG and vaccination administration
7. Vaccination indicated for individuals aged 9 to 26 years
8. Painful vesicular lesions appear at site of contact and can last for 1 to 3 weeks

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

QUESTIONS 9–12

9. A 19-year-old woman, gravida 0, para 0, presents to you because of a 5-day history of frequent urination and dysuria. She was seen by a doctor 2 days ago and prescribed ampicillin. She has no remarkable medical history. She is sexually active and recently began having intercourse with a new boyfriend. She has no known drug allergies. Today her urinalysis shows the following: 2 squamous cells, 0 nitrites, 18 WBC/hpf, 0 bacteria. Her urine human chorionic gonadotropin (hCG) is negative. The next best step in management is:

- ☐ A Ceftriaxone
- ☐ B Trimethoprim–sulfamethoxazole
- ☐ C Spectinomycin
- ☐ D Azithromycin
- ☐ E Observation

10. A 26-year-old woman, gravida 1, para 0, at 14 weeks of gestation, presents to you because of increased vaginal discharge. You perform a wet mount and test for gonorrhea and chlamydia by NAAT. The results of NAAT are positive for chlamydia. The next step in management is (note: TOC = test of cure and RS = rescreen):

- ☐ A Azithromycin (patient and partner) + TOC 5 weeks + RS 4 months
- ☐ B Doxycycline (patient and partner) + TOC 5 weeks + RS 5 months
- ☐ C Ofloxacin (patient and partner) + TOC 4 weeks + RS 4 months
- ☐ D Erythromycin (patient and partner) + TOC 3 weeks + RS 4 months
- ☐ E Erythromycin (patient and partner) + TOC 2 weeks + RS 3 months

11. A 20-year-old presents to you with a deep, excavating, painless lesion above the clitoris, overlying the pubic bone. Her serum VDRL is positive. A lumbar puncture and analysis of her cerebrospinal fluid also yields a positive VDRL. The best term to describe her lesion is:

- ☐ A Condyloma acuminatum
- ☐ B Condyloma latum
- ☐ C Chancre
- ☐ D Gumma
- ☐ E Bubo

12. The most commonly reportable bacterial STD in the United states is:

- ☐ A Gonorrhea
- ☐ B *Chlamydia trachomatis*
- ☐ C Syphilis
- ☐ D Genital warts
- ☐ E Chancroid



Answers and Explanations

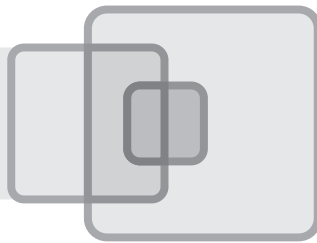
1. **D** [III D], 2. **A** [II C], 3. **C** [II B], 4. **G** [IV A], 5. **H** [VI A], 6. **F** [IV E], 7. **E** [IV B], 8. **B** [IV C]. *H. ducreyi* is the causative organism of chancroid which presents with a painful genital ulcer and is rarely seen in the United States but is the most common cause of genital ulcerative lesions in sub-Saharan Africa. Genital herpes infection starts out as a vesicular lesion and then develops into an ulcerative lesion and will spontaneously resolve after 1 to 3 weeks without treatment. *Chlamydia trachomatis* serotypes L1 to 3 cause lymphogranuloma venereum and secondary genital skin ulceration and damage from abscess rupture caused by lymphatic spread of the disease is not reversed by delayed treatment. Chancre is the presenting lesion of primary syphilis and while it is painless, it is infectious. Currently available quadrivalent HPV vaccination is indicated for both sexes between ages 9 and 26. Immediate newborn prophylaxis with hepatitis B vaccination and antihepatitis B IgG prevents vertical transmission from mothers who are chronic carriers. Treatment of HIV-infected mothers with reduction to nondetectable viral load has been successful in preventing vertical transmission of HIV. Breastfeeding by infected mothers has been associated with infant infection. Permethrin is currently the recommended treatment for pediculosis pubis (“crabs”).

9. **The answer is D** [II B 2]. Symptoms of urethritis (frequency and dysuria) and pyuria (“pus in urine” or many white blood cells in urine) with a negative urine culture in a sexually active woman suggest chlamydial infection. The treatment of choice in a nonpregnant patient is single-dose azithromax or doxycycline. Trimethoprim–sulfamethoxazole can be used for urinary tract infections, although currently it is not the treatment of choice.

10. **The answer is A** [II B 4 and 5 and II A 5]. Although the best studies of management of chlamydia during pregnancy involve an erythromycin base, azithromycin may also be used and is not contraindicated. Both doxycycline and ofloxacin are contraindicated during pregnancy because the former is similar to tetracycline and causes staining of developing teeth, and the latter interferes with cartilage development. The last two answer choices are incorrect because they both perform TOC in less than 4 weeks after treatment. Because nucleic acids test do not test for live organisms, they can remain positive for up to 3 weeks after treatment. Additionally, any treatment used during pregnancy requires TOC and RS.

11. **The answer is D** [III D 2 c]. Neurosyphilis (or tertiary syphilis) is diagnosed by ophthalmic signs in someone whose serum is VDRL positive, or in someone with gummas whose CSF tests positive for VDRL. Condyloma acuminatum (warts) is caused by HPV. Condyloma latum is indicative of secondary syphilis (not tertiary). Painless chancre is a lesion of primary syphilis. Buboec are caused by *Haemophilus ducreyi*, which causes chancroid.

12. **The answer is B.** Chlamydia is the most commonly reported STI worldwide and the most common bacterial STI in the United States. While genital wart infection is more common, the human papilloma virus (not a bacteria) is the cause and genital wart infection is not generally a reportable STI in the United States. Gonorrhea and syphilis are reportable but are less commonly in the United States. Chancroid is rarely seen in the United States.



Pelvic Inflammatory Disease

ANN HONEBRINK

I

INTRODUCTION

Pelvic inflammatory disease (PID) comprises a spectrum of inflammatory diseases of the upper genital tract of women. PID can involve infection of the endometrium (**endometritis**), the oviducts (**salpingitis**), the ovaries (**oophoritis**), the uterine wall (**myometritis**), or portions of the parietal peritoneum (**peritonitis**). PID is usually the result of a sexually transmitted disease (STI) and less often results from iatrogenic causes after instrumentation of the female reproductive tract.

II

DEFINITIONS

- A Acute PID** refers to the acute symptoms accompanying ascending infection from the cervix to the endometrium, tubes, ovaries, and pelvic peritoneum.
- B Chronic PID** refers to chronic pelvic pain, often periodic in exacerbation, which can follow an acute episode of PID, a sequelae to the inflammatory response to an acute infection in the pelvis. Chronic pelvic infection can also be caused by the more rare pelvic infection with tuberculosis (TB) and actinomycosis.
- C Silent PID** refers to asymptomatic or mildly symptomatic pelvic infection, which is usually diagnosed when the sequelae of tubal damage is found at a later date.

III

EPIDEMIOLOGY

- A Incidence** PID is usually a disease of young women. Peak incidence occurs in women in their late teens and early 20s and the majority of cases of PID in the United States are diagnosed in women younger than 25 years of age.
 1. The number of cases of PID in the United States has been declining. An estimated 168,837 cases of PID occurred in the United States in 2003.
 2. US hospitalizations for the diagnosis of PID has also been declining since the 1980s and have leveled off at approximately 70,000 per year since the 1990s.
 3. Aggressive screening for and treatment of asymptomatic gonorrhea and chlamydia is thought to be a major contributing factor to the decline in diagnosis of and hospitalizations for PID.
- B Costs**
 1. Direct and indirect costs of PID and its sequelae are estimated at \$2 billion annually with 70% of these dollars spent on the caring for acute PID.
- C Medical sequelae** develop in one in four women with acute PID.
 1. **Tubal obstruction** is a sequelae of PID and leads to **infertility**. Infertility occurs after acute PID in 6% to 60% of cases, causing more than 100,000 women per year to become infertile. The risk of tubal obstruction depends on the severity and the number of episodes of infection.
 - a. After one episode: 11.4%
 - b. After two episodes: 23.1%
 - c. After three episodes: 54.3%

2. **Ectopic pregnancy rate** increases six- to tenfold in women with PID. Approximately 50% of all ectopic pregnancies are thought to result from the tubal damage caused by PID.
3. **Chronic pelvic pain** develops in 20% of women with acute PID. Both chronic pelvic pain and dyspareunia can be sequelae of PID.
4. **Mortality**, although rare, does occur, particularly in neglected cases in which a **ruptured tubo-ovarian abscess** can lead to septic shock and death. In the United States, more than 150 deaths are attributed to PID annually.

D Sexual activity Women who are not sexually active do not contract PID. Conversely, women who are sexually active but use no contraception contract 3.42 cases of PID per 100 woman-years. Frequent sexual activity, early onset of sexual activity, multiple sex partners, and a recent new sex partner are associated with risk for developing PID.

1. **Male condoms**, when used consistently and correctly, are very effective in preventing PID, as well as other STIs. Latex and polyurethane condoms provide greater protection than natural membrane condoms. **Female condoms** are made of polyurethane, and although little data exist regarding their use and PID, they should reduce chance of transmission of STDs and therefore PID.
2. **Oral contraceptives (OCs)** appear to protect users against PID: only 0.91 case of PID per 100 woman-years has been reported among women using the pill. This relationship between the pill and PID may be the result of sexual factors, including:
 - a. Decreased menstrual flow
 - b. Decreased ability of pathogenic bacteria to attach to endometrial cells
 - c. Progestin-induced changes in the cervical mucus that retard the entrance of bacteria. While OC use seems to be protective against the development of PID, OC users are more likely to screen positive for chlamydia.
3. **Other barrier methods of contraception** (e.g., the diaphragm, sponge, and contraceptive foam) also protect against PID. Spermicides may also be bactericidal. However, more recent studies have shown that spermicide use may actually increase HIV transmission during vaginal intercourse. This limits enthusiasm in recommending spermicides for protection against transmission of STIs in general.
4. **Intrauterine devices (IUDs)** have been linked to an increased risk of PID (5.21 cases per 100 woman-years). Infection in this case may be related to insertion rather than a sexually transmitted infection. The risk is confounded by epidemiologic factors: the risk is lower in monogamous, healthy women and increases with a history of STI and sexual promiscuity. Also, currently utilized IUDs are associated with a lower risk than seen with older-model IUDs.

E Prevention The majority of cases of PID are sexually transmitted and are theoretically preventable. Prevention efforts involve:

1. Education of both the public and providers about healthy sexual behaviors to help avoid transmission of infection
2. Screening of individuals at risk for STDs and provision of timely treatment and education to individuals who screen positive to prevent ascending infection
3. Involving male partners in screening, treatment, and prevention programs to prevent further transmission
4. Prompt treatment of PID to prevent tubal sequelae

IV

BACTERIOLOGY

Acute PID is usually a **polymicrobial infection** caused by gonorrhea, chlamydia, and organisms that are considered normal flora of the cervix and vagina.

A Causative organisms

1. *Neisseria gonorrhoeae* is a Gram-negative diplococcus. Studies show it is recovered from the cervix in 27% to 80% and the fallopian tubes in 13% to 18% of women diagnosed with PID.

2. *Chlamydia trachomatis* is an obligate intracellular organism. It is recovered from the cervix in 5% to 39% and from the tubes in 0% to 10% of women diagnosed with PID. Antibodies to *C. trachomatis* are found in 20% to 40% of women with a history of PID.
3. *N. gonorrhoeae* and *C. trachomatis* coexist in the same individual in 25% to 40% of cases of PID.
4. Once the infection has ascended into the uterus and fallopian tubes the infection is generally polymicrobial. Endogenous aerobic bacteria, such as *Escherichia coli*, *Gardnerella vaginalis*, *Streptococcus species*, *Proteus*, *Klebsiella*, and *Haemophilus influenzae* and endogenous anaerobic bacteria such as *Bacteroides*, *Peptostreptococcus*, and *Peptococcus* have been isolated from the upper genital tract in up to 70% of women diagnosed with PID.
5. *Actinomyces israelii*, which is found in 15% of IUD-associated cases of PID, particularly in unilateral abscesses. It is rarely found in women who do not use an IUD.

V

PATHOPHYSIOLOGY

When PID occurs, salpingo-oophoritis is usually preceded by cervical infection with gonorrhea and/or chlamydia; infection ascends when an inciting event occurs that allows bacteria to ascend into the uterus and then into the tubal lumen, usually bilaterally. Symptomatic ascending infection follows 10% to 40% of cervical infections with gonorrhea and chlamydia.

A Inciting events

1. **Menstrual periods.** Degenerating endometrium is a good culture medium and retrograde menstruation encourages ascending infection. In addition, cervical mucus changes during menses allow ascending infection. Two-thirds of acute PID cases begin just after menses.
2. **Sexual intercourse.** Bacteria-laden fluids may be pushed into the uterus, and uterine contractions may assist their ascent.
3. **Bacterial vaginosis (BV)** is also present in up to two-thirds of women diagnosed with PID. BV is caused by an alteration of the bacterial balance in the vagina with an overgrowth of *Gardnerella vaginalis* and *Mycoplasma* organisms. These organisms can break down naturally protective cervical mucus. BV both facilitates ascending spread of vaginal microorganisms by interfering with normal vaginal and cervical defenses to ascending infection and also provides potentially infecting organisms.
4. **Iatrogenic events**
 - a. Elective abortion
 - b. Dilation and curettage or endometrial biopsy
 - c. IUD insertion or use
 - d. Hysterosalpingography
 - e. Chromopertubation at laparoscopy

B Chronology of salpingo-oophoritis Infection is usually bilateral, but unilateral infection is also possible, especially in association with an IUD. The **clinical course** is as follows:

1. **Endosalpingitis** develops initially with edema and ultimately proceeds to destruction of luminal cells, cilia, and mucosal folds. Bacterial toxins are most likely to be responsible.
2. Infection spreads to the tubal muscularis and serosa. It also spreads by direct extension to the abdominal cavity through the fimbriated end of the tube.
3. **Oophoritis** develops over the surface of the ovaries, and microabscesses may develop within the ovaries.
4. **Peritonitis** may occur, and upper abdominal infection may result either by direct extension of infection up the abdominal gutters laterally or by lymphatic spread. Development of **perihepatitis** with adhesions and right upper quadrant abdominal pain is known as **Fitz–Hugh–Curtis syndrome**.
5. **Sequelae of PID**
 - a. Pyosalpinges (tubal abscesses)
 - b. Hydrosalpinges (fluid-filled, dilated, thin-walled, destroyed tubes, usually totally obstructed)

- c. Partial tubal obstruction and crypt formation
- d. Total tubal obstruction and infertility
- e. Tubo-ovarian abscesses
- f. Peritubal and ovarian adhesions
- g. Dense pelvic and abdominal adhesions
- h. Ruptured abscesses, resulting in sepsis and shock
- i. Chronic pelvic pain and dyspareunia

VI

DIAGNOSIS

A **Signs and symptoms of PID** are relatively nonspecific. Thus, they produce both a high false-positive rate and a high false-negative rate of diagnosis. Laparoscopic studies have revealed the inadequacy of diagnosing acute PID by means of the usual history and physical examination and laboratory studies (Table 34–1). In studies using laparoscopic confirmation, the clinical diagnosis of PID only has a two-thirds positive predictive value. In order to prevent sequelae of PID, it is appropriate to maintain a high index of suspicion and low threshold for treatment once other serious causes for symptoms have been ruled out.

B **Clinical criteria for diagnosis**

1. Minimum criteria for diagnosis

- a. Lower abdominal tenderness
- b. Uterine or adnexal tenderness
- c. Cervical motion tenderness: lateral motion of the cervix on examination causes pain by putting tension on the adnexa

2. Additional criteria. For women with severe signs, these additional criteria are used to increase the specificity of the diagnosis:

- a. Oral temperature higher than 100.9°F (38.3°C) present in less than one-third of women diagnosed with PID
- b. Abnormal cervical or vaginal discharge. Mucopurulent cervical discharge with white blood cells (WBCs) seen on wet mount is almost always seen in women with PID. If this finding is not present, other diagnoses should be seriously entertained
- c. Elevated erythrocyte sedimentation rate (ESR)
- d. Elevated C-reactive protein
- e. Positive test for gonorrhea or chlamydia
- f. Tubo-ovarian abscess seen on ultrasound
- g. Evidence of endometritis on endometrial biopsy
- h. Laparoscopic evidence of PID

TABLE 34–1 Laparoscopic Findings in Patients with False-Positive Clinical Diagnosis of Acute Pelvic Inflammatory Disease

Laparoscopic Finding	Number of Patients
Acute appendicitis	24
Endometriosis	16
Corpus luteum bleeding	12
Ectopic pregnancy	11
Pelvic adhesions only	7
Benign ovarian tumor	7
Chronic salpingitis	6
Miscellaneous	15
Total	98

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3. Other symptoms that may be seen in women with PID include
 - a. Abdominal pain
 - b. Intermenstrual and/or postcoital bleeding
 - c. Urinary frequency
 - d. Nausea/vomiting
 - e. Lower back pain

C **Differential diagnosis** for PID should include:

1. Ectopic pregnancy
2. Ruptured ovarian cyst
3. Appendicitis
4. Endometriosis
5. Inflammatory bowel disease
6. Degenerating fibroids
7. Spontaneous abortion
8. Diverticulitis

D **Diagnostic techniques**

1. **Cervical Gram stain.** If Gram-negative intracellular diplococci are present, gonorrhea is the presumed diagnosis. However, Gram stain alone misses one-half of the gonorrhea cases. Chlamydia is not diagnosed on Gram stain.
2. **Serum human chorionic gonadotropin (hCG).** A sensitive pregnancy test is important in the differential diagnosis of pelvic pain to rule out the possibility of ectopic pregnancy. In the past, approximately 3% to 4% of women admitted with the diagnosis of PID had an ectopic pregnancy.
3. **Ultrasound.** This technique may help define adnexal masses and intrauterine or ectopic pregnancies, especially when a patient has a tender abdomen that does not permit an adequate pelvic examination. This is important for detecting the presence of tubo-ovarian abscesses since antibiotic therapy protocols may be different from PID without tubo-ovarian abscesses. Response to therapy can be measured objectively as pelvic masses and induration regress.
4. **CT scan** of the abdomen and pelvis can also be helpful in ruling out appendicitis.
5. **Laparoscopy.** If the disease process is unclear, this technique is the ultimate way to establish the diagnosis.
6. **Blood studies**
 - a. **Leukocytosis** is not a reliable indicator of acute PID. Less than 50% of women with acute PID have a WBC count greater than 10,000 cells/mL. Also, it is nonspecific; other infectious causes of symptoms are associated with an elevated WBC count.
 - b. An **increased ESR** is a nonspecific finding, but the ESR is elevated in approximately 75% of women with laparoscopically confirmed PID.
7. **Follow-up.** After initiation of appropriate treatment, clinical improvement should be observed in 48 to 72 hours. If no improvement occurs, alternative diagnoses should be considered.
8. **Testing** for HIV and assurance of current Pap smear screening should be offered to all women diagnosed with PID. Additionally, testing for syphilis and hepatitis B should be considered.

VII

TREATMENT

- A** **Empiric treatment** of PID should be given to women with historic risk factors for PID (either sexual activity or instrumentation of the cervix and uterus) if the minimal clinical criteria are met. Treatment of the woman's partner(s) is also critical to prevent reinfection and prevent potential further spread of infection.

B Individualized treatment and a **high index of suspicion for infection** are mandatory. Treatment should always include sexual partners. The physician must decide between outpatient management of the woman, with close follow-up in 48 to 72 hours, or hospitalization. **Hospitalization of PID patients** and intravenous antibiotic therapy is indicated in the following scenarios:

1. Until other serious diagnoses are excluded, including appendicitis and ectopic pregnancy
2. If the patient is an adolescent
3. If a pelvic abscess is suspected on examination or ultrasound
4. Severe systemic/peritoneal symptoms including high fever, or signs of peritonitis
5. Inability to tolerate oral outpatient treatment because of vomiting
6. If the patient is pregnant
7. If the patient is unable or unlikely to comply with outpatient therapy and/or 48- to 72-hour follow-up
8. If HIV infection is present
9. If the patient has not responded to outpatient management at 48- to 72-hour follow-up

C Oral treatment regimens provide broad coverage for organisms frequently isolated from the genital tracts of women with PID. They are generally appropriate for women who present with milder cases of PID. Select **one** of the following three regimens:

1. **Ceftriaxone** 250 mg intramuscular single dose *or* **cefoxitin** 2 g intramuscular single dose with probenecid 1 g orally at the time of injection *or* **other third-generation cephalosporin**
2. *Plus* **doxycycline** 100 orally twice daily for 14 days, with or without **metronidazole** 500 mg twice daily for 14 days to treat chlamydia and BV
3. Fluoroquinolones are no longer recommended as a component of treatment of PID secondary to increased emergence of quinolone-resistant gonorrhea.

D Parenteral regimens are generally used in women with more severe PID. Randomized trials have demonstrated the efficacy of both oral and parenteral treatment regimens but have not compared oral and parenteral regimens objectively. Parenteral treatment is generally continued for at least 24 hours after significant clinical improvement has occurred. After this, conversion is made to an oral regimen, which is continued for an additional 10 to 14 days. Regimens are designed to cover both *N. gonorrhoeae* and *C. trachomatis* as well as other commonly isolated organisms.

1. **Regimen A.** Use one of the following:
 - a. **Cefotetan** 2 g intravenously every 12 hours *or* **cefoxitin** 2 g intravenously every 6 hours.
 - b. *Plus* **doxycycline** 100 mg orally or intravenously every 12 hours. Both the oral and intravenous routes of doxycycline provide similar bioavailability, and considerable pain is usually associated with intravenous administration of doxycycline. Once parenteral therapy is discontinued, oral doxycycline should be continued for a total of 10 to 14 days. Oral clindamycin or metronidazole may be added to doxycycline if an abscess is suspected.
2. **Regimen B.** Use one of the following:
 - a. **Clindamycin** 900 mg intravenously every 8 hours *plus* **gentamicin** 2 mg/kg loading dose intravenously or intramuscularly followed by 1.5 mg/kg maintenance dose every 8 hours.
 - b. When **conversion to oral therapy** takes place, doxycycline 100 mg twice daily or clindamycin 450 mg four times daily can be used. Clindamycin is usually the favored agent when a tubo-ovarian abscess is suspected and doxycycline is favored when chlamydia infection is suspected or confirmed on testing.

E Treatment regimens for tubo-ovarian abscess (TOA) The diagnosis of TOA may be suspected on examination and then generally confirmed on ultrasound. TOA should also be suspected when there is not prompt response to standard treatment. Since the bacterial flora in tubo-ovarian abscesses is mostly a mixture of Gram-positive, Gram-negative, and anaerobic flora, broad-spectrum antibiotics that cover these organisms should be chosen.

1. **Ampicillin** 2 g intravenously every 4 hours, *plus* **gentamicin** standard dose, *plus* **metronidazole** 500 mg intravenously every 8 hours

2. **Ofloxacin** 400 mg intravenously every 12 hours, *plus* **metronidazole** 500 mg intravenously every 8 hours
3. Single-agent therapy
 - a. **Ticarcillin clavulanate** 3.1 g intravenously every 4 hours
 - b. **Piperacillin-tazobactam** 4 g/0.5 g intravenously every 8 hours
 - c. **Imipenem cilastatin** 500 mg intravenously every 6 hours

F Surgical intervention In cases of severe PID, especially when tubo-ovarian abscess is present, consideration should be given to surgical intervention if the patient's condition worsens or fails to improve after around 72 hours of treatment.

1. **Laparoscopy** may be considered for diagnosis and may be followed by laparotomy. Unless a well-defined unilateral abscess allows a unilateral salpingo-oophorectomy, the treatment of choice is a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and drainage of the pelvic cavity. The patient, regardless of age, should be prepared for this possibility before surgery.
2. If an abscess is accessible, then **catheter drainage** may be possible via transvaginal, transabdominal, or transgluteal access.

VIII OTHER CAUSES OF PELVIC INFECTION

A Granulomatous salpingitis

1. **Tuberculous salpingitis** almost always represents systemic TB. The incidence is high in underdeveloped countries and low in developed countries. It usually affects women in their reproductive years, but an increased incidence has been reported among postmenopausal women. Primary genital TB is extremely rare in the United States.
 - a. **Physical findings** are variable. Patients usually present with adnexal masses. Induration may be noted in the paracervical, paravaginal, and parametrial tissues. The typical patient is 20 to 40 years of age with known TB and a pelvic mass. Symptoms are related to a family history of TB, low-level pelvic pain, infertility, and amenorrhea.
 - b. **Pathology.** Grossly, the uterine tube has a classic "tobacco pouch" appearance—enlarged and distended. The proximal end is closed, and the fimbriae are edematous and enlarged. Microscopically, tubercles show an epithelioid reaction and giant cell formation. Inflammation and scarring are intense and irreversible.
 - c. **Treatment** involves the standard regimens for disseminated TB, including isoniazid, rifampin, and ethambutol. Prognosis for cure is excellent, but the outlook for fertility is dismal.
2. **Leprous salpingitis.** The histologic picture is similar to the one for TB, and the two are often difficult to distinguish on a histologic basis. Langerhans giant cells and epithelioid cells are present. Positive cultures are necessary for a diagnosis of TB.
3. **Actinomycosis.** *Actinomyces israelii*, the causative agent, is pathogenic for humans but not for other mammals. Most gynecologic involvement is infection secondary to appendiceal infection, gastrointestinal tract disorders, or IUD use. A total of 100 cases are reported annually, and the age range of prevalence is about 20 to 40 years.
 - a. **Physical findings.** Half the lesions are bilateral and are characterized by adnexal enlargement and tenderness. Presenting symptoms may be confused with those of appendicitis.
 - b. **Pathology.** Grossly, there is tubo-ovarian inflammation, as well as copious necrotic material on sections of the tube. The tubal lumen may have an adenomatous appearance. Microscopically, actinomycotic "sulfur" granules are present. Club-like filaments radiate out from the center. A monocytic infiltrate is apparent, and giant cells may be present.
 - c. **Treatment.** Therapy is a prolonged course of penicillin.
4. **Schistosomiasis** occurs most commonly in the Far East and Africa.
 - a. **Physical findings** are pelvic pain, menstrual irregularity, and primary infertility. The diagnosis is usually made by histopathologic findings.
 - b. **Pathology.** Grossly, lesions appear as a nonspecific tubo-ovarian process. Microscopically, the ova or schistosome is seen surrounded by a granulomatous reaction with giant and epidermoid cells. An egg within an inflammatory milieu is a dramatic sight.

5. **Sarcoidosis.** Although rare, sarcoidosis can lead to a granulomatous salpingitis.
6. **Foreign body salpingitis** occurs after the use of non-water-soluble dye material for hysterosalpingography. It may also be secondary to medications placed within the vagina, such as starch, talc, and mineral oil.

B **Nongranulomatous salpingitis** refers to any other bacterial infection, usually of the peritoneal cavity, that can secondarily cause tubal infection, including:

1. Appendicitis
2. Diverticulitis
3. Crohn disease
4. Cholecystitis



Study Questions for Chapter 34

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A 19-year-old woman, whose last menstrual period (LMP) was 32 days ago and who is sexually active, presents to the emergency department reporting a 5-day history of lower abdominal pain. Her vitals are as follows: T = 101°F, BP = 110/75, P = 80, R = 16. Speculum examination reveals purulent exudate at the cervical os, and there is cervical motion tenderness. Bimanual examination is unremarkable for masses but produces severe discomfort. Her quantitative serum hCG = 150 mIU/mL. Urinalysis is normal. Her WBC count is 14,000. An office ultrasound shows a normal-sized, normal-striped uterus and no adnexal masses. The next best step in management of this patient is:

- ☐ A Repeat serum hCG in 48 hours
- ☐ B Penicillin G intravenously
- ☐ C Ampicillin and gentamicin intravenously
- ☐ D Clindamycin and gentamicin intravenously
- ☐ E Cefazolin and doxycycline intravenously

2. Which one of the following statements about bacterial involvement with PID is correct?

- ☐ A *Chlamydia trachomatis* is found in 20% to 40% of cervical specimens with PID
- ☐ B *N. gonorrhea* is recovered from the cervix in up to 20% of cases of PID
- ☐ C *H. influenzae* is found in 15% of IUD-associated PID
- ☐ D *E. coli* is the most common anaerobic bacteria identified in PID
- ☐ E *N. gonorrhea* and *C. trachomatis* coexist in 25% to 40% of cases of PID

3. A 17-year-old woman has symptoms suggestive of pelvic inflammatory disease. However, the patient is adamant that she is a virgin. If the signs of PID are present because of inflammation involving the uterus, tubes, and ovaries, the most likely diagnosis is:

- ☐ A Tuberculosis
- ☐ B Endomyometritis
- ☐ C Schistosomiasis
- ☐ D Appendicitis
- ☐ E Ectopic pregnancy

QUESTIONS 4–5

A 22-year-old woman, gravida 1, para 0, total abortions 1, presents to the emergency department reporting a 6-day history of lower abdominal pain and purulent vaginal discharge. She denies past medical history or surgery. Her vitals are as follows: T = 102°F, BP = 118/78, P = 96, R = 14. Her abdomen is without scars, bowel sounds are present, and there is tenderness in the lower pelvic region of the abdomen. However, there is no rebound tenderness or guarding. Her speculum examination reveals white exudate at the external os of the cervix. Bimanual examination reveals severe cervical motion tenderness and uterine tenderness. There is also a fullness in the left adnexa. Her urine hCG is negative, and WBC count = 15,000.

4. The next best step in management is:

- ☐ A Pelvic ultrasound
- ☐ B Computed tomography scan
- ☐ C Quantitative serum b-hCG
- ☐ D Immediate hospitalization
- ☐ E Ceftriaxone intramuscularly plus doxycycline orally

5. The most important reason to admit this patient to the hospital is:

- ☐ A WBC count
- ☐ B Temperature
- ☐ C Pelvic examination
- ☐ D Age of patient
- ☐ E Patient is unreliable



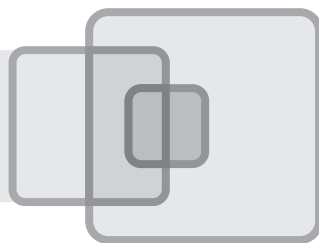
Answers and Explanations

1. **The answer is D** [VI D 2]. This patient has acute PID and she happens to be pregnant at the same time. Currently, there are no signs or risk factors for an ectopic pregnancy and with an LMP of 32 days and an hCG = 150, the pregnancy is too early to visualize on ultrasound. Intravenous clindamycin and gentamicin is an appropriate combination for parenteral treatment of PID because this patient is pregnant. This regimen provides anaerobic, aerobic, *N. gonorrhoeae*, and *C. trachomatis* coverage. Penicillin resistance is common in gonorrhea, which makes penicillin alone and the ampicillin and gentamicin combination inappropriate. The use of doxycycline is contraindicated in pregnancy because, like tetracycline, it can stain developing teeth. Resistance to second-generation cephalosporins is increasingly common in endogenous bacteria found in PID as well as gonorrhea.

2. **The answer is E** [IV]. *N. gonorrhea* and *C. trachomatis* coexist in 25% to 40% of cases of PID. It is therefore important to treat both of these organisms when one is found. *C. trachomatis* is recovered from the cervix in 5% to 39% and from the tubes in 0% to 10% of women, but antibodies to *C. trachomatis* are found in 20% to 40% of women. *N. gonorrhea* is recovered from the cervix in 27% to 80% of cases and from the tubes in approximately 20%. *E. coli* is an aerobic bacteria commonly seen with PID. *Actinomyces israelii* is found in 15% of cases of IUD-associated PID.

3. **The answer is D** [VI C and Table 34–1]. Inflammation of the tubes and ovaries can be seen in conjunction with any of the conditions listed. The bacterial infection involved in appendicitis can cause secondary tubal infection and is the most likely diagnosis. Patients with false-positive diagnosis of PID were found at laparoscopy to have appendicitis (#1), endometriosis (#2), corpus luteum bleeding (#3), and ectopic pregnancy (#4). Schistosomiasis and tuberculosis are rare in the United States. Endomyometritis usually occurs postpartum, usually as a complication of cesarean section in a patient with prolonged rupture of membranes.

4. **A** [VI B to D], 5. **C** [VI B to D]. Because this patient has symptoms and signs of PID along with an adnexal mass, the next few management steps all depend on an ultrasound examination. You must evaluate for a tubo-ovarian abscess (i.e., adnexal mass on ultrasound) before diagnosing a patient with uncomplicated PID and sending her home on oral treatment. However, if an adnexal mass is seen on ultrasound, it could be either a mass (cyst or tumor) or a tubo-ovarian abscess. Such a patient must be admitted to the hospital and placed on intravenous antibiotics. Surgical exploration should be considered if she does not respond to intravenous antibiotic therapy in 48 to 72 hours. A computed tomography scan is not as useful as an ultrasound in this situation. There is no need for a quantitative hCG when the ultra-sensitive urine hCG (which can detect as low as 5 mIU/mL) is negative. A tubo-ovarian abscess or pelvic abscess may first be appreciated on pelvic examination and can be further evaluated with an ultrasound. The history does not suggest that the patient is unreliable. The other answer choices are not criteria for hospitalization and intravenous antibiotic therapy (although some clinicians may consider her temperature as a reason to hospitalize).



Vulvovaginitis

DACARLA M. ALBRIGHT

I

INTRODUCTION

Vulvovaginitis is an extremely common gynecologic problem. A broad spectrum of disorders may produce vulvovaginal symptoms, including infections, dermatologic conditions, benign and malignant neoplasms.

II

VULVOVAGINAL ANATOMY

A Vulva This is the external aspect of the female genitalia. It is made up of the **mons pubis**, **labia majora** and **minora**, **clitoris**, and the **vestibule**. It also contains the urinary meatus and the vaginal orifice, as well as the glands of the vulva: Bartholin glands (major vestibular glands), ducts of the Skene glands (paraurethral glands), and minor vestibular glands (Fig. 35–1).

1. Anatomy

- a. The entire vulva is covered by a **keratinized** squamous epithelium.
 - b. Hair-bearing regions contain hair follicles, sebaceous glands, apocrine, and eccrine sweat glands.
 - c. The labia minora and prepuce (the hood of the clitoris), are hairless regions which contain sebaceous glands but not hair follicles, eccrine or apocrine sweat glands.
 - d. The **labia majora** are composed of skin enclosing a variable amount of fat and smooth muscle.
 - (1) They extend from the mons pubis anteriorly to the fourchette posteriorly.
 - (2) The embryologic homolog in the male is the scrotum.
 - e. The **labia minora** are erectile tissue, devoid of fat and composed of skin and vascular and connective tissue.
 - (1) They extend from the prepuce two-thirds of the distance of the perineum.
 - (2) The embryologic homolog in the male is the floor of the penile urethra.
 - f. The **clitoris** is a highly vascular and innervated, erectile organ 2 to 3 cm in length, located between the bifurcating folds of the labia minora.
 - (1) It consists of the glans and the body, covered by the prepuce.
 - (2) The embryologic homolog in the male is the penis.
 - g. The **vestibule** is the space between the labia minora extending from the clitoris to the vaginal introitus. It contains the urethral meatus and the openings of the major and minor vestibular glands as well as the Skene glands.
 - h. **Bartholin glands** are the major vestibular glands.
 - (1) They lie posterior and lateral to the vaginal introitus.
 - (2) The embryologic homolog in the male is the Cowper glands.
 - i. **Ducts of the Skene glands** and **minor vestibular glands** are paraurethral structures.
2. **Nerve supply.** The nerve supply to the vulva includes sensory nerves, special receptors, and autonomic nerves to vessels and glands. Symptoms of vulvovaginal disorders are frequently caused by irritation of the sensory nerves of the vulva. The major nerves supplying the vulva include those derived from the pudendal, ilioinguinal, genitofemoral, and posterior femoral cutaneous nerves.

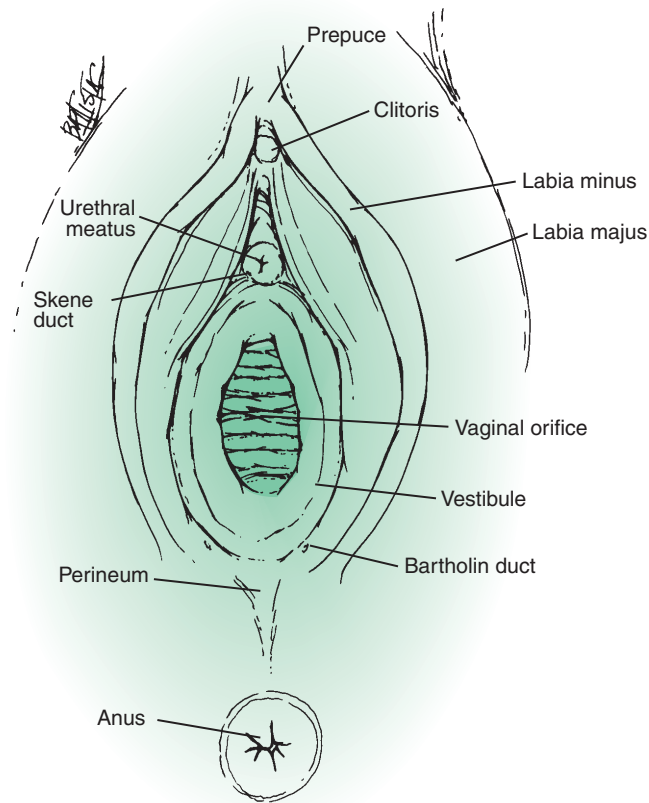


FIGURE 35–1 Anatomic structures of the vulva.

- a. The **pudendal nerve** gives rise to the inferior hemorrhoidal nerve, the perineal nerve, and the dorsal nerve of the clitoris.
- b. The **ilioinguinal nerve** gives rise to the anterior labial nerves.
- c. The **genitofemoral nerve** has a genital branch which innervates the anterior vulva.
- d. The **posterior femoral cutaneous nerve** gives rise to the posterior labial nerves.
3. **Vascular supply.** The major blood vessels supplying the vulva derive from the internal pudendal artery, which arises from the internal iliac artery, and the superficial and deep external pudendal arteries, which arise from the femoral artery.
4. **Lymphatic supply.** The femoral and inguinal lymph nodes receive the lymphatic drainage from the vulva. The superficial inguinal lymph nodes are the initial site of drainage. Many infections or inflammatory conditions of the vulva and distal vaginal wall are accompanied by an increase in lymphatic drainage, resulting in tender lymphadenopathy at this site.

B Vagina This structure is a hollow cylinder approximately 9 to 10 cm in length. It extends from the introitus to the uterus and lies dorsal to the bladder and ventral to the rectum.

1. **Anatomy.** The vaginal wall has three layers: the mucosa, muscularis, and adventitia.
 - a. The **mucosa** is covered by a stratified, **nonkeratinized**, squamous epithelium.
 - (1) It is a mucous membrane that is under the hormonal influence of the ovarian steroids. **Estrogen stimulates** the proliferation and maturation of vaginal epithelial cells, whereas progesterone is inhibitory.
 - (2) There are no glandular structures. Endocervical and Bartholin gland secretions, with the **transudation of fluid** across the vaginal epithelium provide lubrication.
 - b. The **muscularis** is composed of an outer longitudinal and inner circular layer.

- c. The **adventitia** is a strong sheet of connective tissue, condensed anteriorly to form the pubo-cervical fascia, and fused to the fascial coverings of the pelvic and urogenital diaphragms.
2. **Nerve supply.** The nerve supply is derived from the lumbar plexus and the pudendal nerve. The pudendal nerve does not have as rich a distribution of fine sensory nerves as the nerves supplying the vulva.
3. **Vascular supply.** The major vessels supplying the vagina include the vaginal artery, arising from the internal iliac or uterine artery; the azygous artery of the vagina, arising from the cervical branch of the uterine artery; and branches of the pudendal artery. Venous drainage forms a plexus surrounding the vagina, and major vessels follow the arterial course.
4. **Lymphatic supply.** The lymphatic drainage of the vagina includes a complex anastomotic plexus that involves drainage to the internal iliac, pelvic, sacral, inferior gluteal, anorectal, femoral, and inguinal nodes.

III

VAGINAL PHYSIOLOGY

The vaginal ecosystem is a finely balanced environment maintained by a complex interaction among vaginal flora, microbial by-products, estrogen, and host factors. The vagina is **usually resistant to infection** for two reasons: **marked acidity** and a **thick protective epithelium**. Other host factors, such as the immune system, also play a role in vaginal defense mechanisms.

A Microbiology The vaginal flora play a critical role in vaginal defenses by maintaining the normally acidic pH (3.8 to 4.2) of the vagina.

1. Normally, 5 to 15 different bacterial species (e.g., group B streptococcus, *Escherichia coli*, *Prevotella*), both aerobic and anaerobic, inhabit the vagina. The type and number may vary in response to normal and abnormal changes in the vaginal environment.
2. ***Lactobacillus acidophilus*** is the dominant bacterium in a healthy vaginal ecosystem. Lactobacilli play a critical role in maintaining the normal vaginal environment.
 - a. The acidic environment of the vagina is maintained through the production of lactic acid.
 - b. Lactic acid and hydrogen peroxide produced by lactobacilli are toxic to anaerobic bacteria in the vagina.
3. **Insults that affect the acidic pH** and lead to a more alkaline environment result in a decrease in lactobacilli, with an overgrowth of pathogenic organisms.

B Host factors

1. **Normal estrogen levels** are necessary for a normal vaginal environment and resistance to infection.
 - a. Estrogen stimulates proliferation and maturation of the vaginal epithelium, providing a physical barrier to infection. Conditions associated with decreased estrogen levels are associated with an increase in susceptibility to vaginal infections.
 - b. Mature vaginal epithelium provides **glycogen**, necessary for lactobacillus metabolism. Glycogen is converted to lactic acid by lactobacilli and vaginal epithelial cells. If glycogen levels are decreased, lactobacillus counts decrease as well.
2. **Cellular and humoral immunity** play a role in the normal vaginal defense mechanisms.

C Factors that alter the vaginal environment Insults that affect the vaginal microbiology, vaginal epithelium, or vaginal pH lead to an increased susceptibility to vaginal infections.

1. **Antibiotics** alter the microbiology of the vagina and can increase the risk of infection.
2. **Hormonal changes** may affect the vaginal epithelium and increase the risk of infection (e.g., decreased estrogen level, increased progesterone level).
3. **Douching or intravaginal medications** can change the vaginal pH or affect the vaginal flora, altering the resistance to infection.
4. **Intercourse** affects the microenvironment of the vagina because semen has an alkaline pH. In addition, intercourse may introduce new organisms into the vagina, thus influencing the microenvironment.

5. **Sexually transmitted infections (STIs)** affect the microbiology of the vagina, changing the resistance to infection. Other organisms may be the cause of vaginal symptomatology.
6. **Stress, poor diet, and fatigue** probably play a role by affecting microbiology, pH, and the immune system.
7. **Foreign bodies** alter the pH and microbiology of the vagina.
8. Changes in immune function associated with **HIV infection** are associated with recurrent vaginal candidiasis.

IV

DIAGNOSIS

A thorough history, a physical examination, and judicious use of ancillary tests are critical to attaining the correct diagnosis. The medical history is essential in evaluating the potential causes of vulvovaginal symptoms. The patient's symptomatology is also important.

A History Certain conditions may predispose women to certain types of vulvovaginal infections. Inciting factors may also indicate other causes, such as allergic reactions. Physicians should consider the following factors:

1. **Sexual activity**
 - a. Are there complaints of irritation?
 - b. What is the relation of the onset of symptoms to intercourse or other sexual activity?
 - c. Has the patient engaged in any unusual sexual practices or had new partners?
2. Onset, intensity, and progression of symptoms
3. Recent systemic or local infection
4. Use of antibiotics
5. History of diabetes mellitus
6. Previous vulvovaginal infections
7. Vaginal hygienic practices (e.g., douching)
8. Contraceptive methods
9. Menstrual history
10. Previous treatments; use of self-prescribed medications, herbal remedies, or home remedies
11. Any other factors that may have altered the vaginal environment

B Symptomatology

1. **Vulvar symptoms.** The two **most common symptoms** are:
 - a. **Burning.** Vulvar irritation or burning is a symptom associated with a variety of disorders, including vulvovaginitis, vulvovestibulitis, and vulvodinia.
 - b. **Itching or pruritus.** Vulvar pruritus is a common symptom that may result from vulvovaginitis. Other possible causes include any skin disorder associated with pruritus, including allergic reactions.
2. **Vaginal discharge.** Description of the discharge is crucial to diagnosis and to the differentiation from a normal physiologic finding. Characteristics include:
 - a. **Consistency (thick, watery).** A thin, white discharge is often normal.
 - b. **Viscosity.** Cervical mucus normally changes during the menstrual cycle. Follicular-phase mucus is normally watery and abundant; postovulatory mucus can be thick and viscous. Patients may observe such changes and report them as abnormal.
 - c. **Color.** Normal discharge is usually white to beige. Green, yellow, or brown discharge is usually associated with an infection, a foreign body, or some other abnormality.
3. **Odor.** Description of the odor is useful in establishing a differential diagnosis.
 - a. An odor may be present without an associated discharge noticed by the patient.
 - b. Complaints of severe, offensive odor occur most often with retained foreign bodies, such as tampons.

V

PHYSICAL EXAMINATION

- A Pelvic examination** is essential in the management of vulvovaginitis and should consist of a thorough evaluation.
1. Inspection of the **external genitalia** detects gross lesions, edema (and discoloration) of the labia, inflammation, ulceration, and condylomata. It also rules out pubic lice.
 2. The **inguinal area** should be palpated for the presence or absence of lymphadenopathy. Any discoloration should be noted.
- B Speculum examination**, using water as the only lubricant to avoid interfering with specimen collection and culturing, should reveal:
1. **Nature of the vaginal discharge** (e.g., consistency, viscosity, color, and odor)
 2. **Evidence of trauma, congenital abnormalities, or characteristic lesions of the vaginal walls** (e.g., “strawberry spots” if *Trichomonas vaginalis* is suspected)
 3. **Presence or absence of cervical abnormalities**. A culture of the endocervix detects gonorrhea or chlamydial infection, and a Papanicolaou test (Pap smear) detects carcinoma or inflammation.
- C Laboratory tests**
1. When an infectious vaginitis is suspected, **vaginal pH** helps differentiate the various types of infections.
 2. A specimen should be obtained for **wet mount preparation**. Microscopic inspection of the vaginal secretions in saline and a 10% potassium hydroxide (KOH) solution is pivotal when diagnosing vaginitis.
 3. Occasionally, **cultures** are useful in difficult cases.

VI

VULVOVAGINAL CONDITIONS (TABLE 35–1)

Vaginitis is characterized by one or more of the following symptoms: increased volume of discharge; abnormal color (yellow or green) of discharge; vulvar itching, irritation, or burning; dyspareunia; and malodor. Vaginitis may be caused by infectious agents (e.g., *Candida*, *Gardnerella*, and *Trichomonas*) or by atrophic changes. Symptoms of other vulvovaginal conditions, including vulvar dystrophies, vulvar dermatitis, and other skin conditions of the vulva, may be similar to those of vaginitis. Acute herpes simplex genitalis may cause acute vulvar symptoms, necessitating prompt evaluation and treatment.

TABLE 35–1 Signs, Symptoms, and Diagnosis of Vulvovaginitis

Etiology	Symptoms	Clinical Signs	Diagnostic Method
Monilial vaginitis	Pruritus	Thick white discharge; pH 4.0–4.7	Wet mount preparation or KOH preparation (pseudohyphae)
<i>Trichomonas</i>	Malodorous discharge, pruritus	Frothy, copious yellow-green discharge; pH 5.0–7.0	Wet mount preparation (motile trichomonads)
Bacterial vaginosis	Discharge, fishy odor	Thin, gray discharge; pH 5.0–5.5	Wet mount preparation, sniff test (clue cells)
Chlamydia	Discharge	Mucopurulent discharge, cervical erosion	Culture; MicroTrak or Chlamydiazyme
Gonorrhea	Discharge	Cervical discharge	Cervical culture; Gram stain
Genital herpes	Pain	Ulcerative, vulvar vesicles and ulcers	Virus culture, Tzanck preparation
Chemical	Discharge	Erythema; may be ulcerative	History and exclusion of other causes
Physiologic	Discharge	No odor or erythema	Wet mount preparation; history, exclusion of other causes; cervical culture

KOH, potassium hydroxide.

A **Bacterial vaginosis** is the most common vaginal infection in the United States today. In the past, bacterial vaginitis was known as nonspecific vaginitis and *Gardnerella* vaginitis.

1. Etiology

- a. Bacterial vaginosis is a polymicrobial clinical syndrome caused by an **overgrowth of a variety of bacterial species**, particularly **anaerobes**, often found normally in the vagina. Organisms most often involved include *Bacteroides*, *Peptostreptococcus*, *Gardnerella vaginalis*, and *Mycoplasma hominis*.
- b. The anaerobic bacteria produce enzymes that break down peptides to amino acids and amines, resulting in compounds associated with the discharge and odor characteristic of this infection.

2. **Clinical presentation.** Fifty percent of women with bacterial vaginosis are asymptomatic. In symptomatic patients, the most common presentation is a malodorous, gray discharge.

3. **Diagnosis.** Three of the following four criteria must be present:

- a. The vaginal pH is generally between 5.0 and 5.5.
- b. Wet mount preparations with saline reveal a “clean” background with **minimal or no leukocytes**, an abundance of bacteria, and the characteristic **clue cells**. The clue cells are squamous cells in which coccobacillary bacteria have obscured the sharp borders and cytoplasm.
- c. Application of 10% KOH to the wet mount specimen produces a **fishy odor**, indicating a positive “whiff” test.
- d. A gray, homogenous, malodorous discharge is present.

4. **Treatment.** Therapy is based on the use of agents with anaerobic activity and involves both topical and systemic agents. The combination appears to be 90% effective.

a. Vaginal preparations

- (1) Intravaginal 2% **clindamycin cream** is used at bedtime for 7 days, or 100 mg ovules vaginally at bedtime for 3 days.
- (2) Intravaginal **metronidazole** is applied once a day for 5 days.

b. Oral regimens

- (1) **Metronidazole** 500 mg twice daily for 7 days; the 2-g single dose regimen is an option, though it may be the least effective method. Avoidance of alcohol during and within 24 hours after use is recommended.
- (2) **Clindamycin**, 300 mg twice daily for 7 days (may be associated with diarrhea, especially *Clostridium difficile*).

c. Routine treatment of partners has not been shown to improve cure rates or lower reinfection rates, and is therefore not recommended.

d. Treatment during pregnancy is critical; data suggest an association of adverse maternal and fetal outcomes with bacterial vaginosis (e.g., preterm birth, premature rupture of the membranes, chorioamnionitis).

- (1) Clindamycin (oral) may be used throughout pregnancy. Vaginal forms should not be used after the second half of pregnancy.
- (2) Metronidazole may be used after the first trimester.

e. Patients with recurrences should be screened for STDs.

B **Candida vaginitis (candidiasis or moniliasis)** is the second most common vaginal infection in the United States. At least 75% of women will experience one episode in their lifetime.

1. Etiology

- a. The etiologic agent is a yeast (fungi) organism, usually *Candida albicans*. The organism is a common inhabitant of the bowel and perianal region. Thirty percent of women **may have vaginal colonization and have no symptoms of infection**.
- b. Several factors may lead to symptomatic infection instead of colonization.
 - (1) Contraceptive practices (e.g., birth control pills and vaginal spermicides, which influence vaginal pH).
 - (2) Use of systemic steroids, which influence the immune system.
 - (3) Use of antibiotics, which alters the microbiology of the vagina; 25% to 70% of women report yeast infections after antibiotic use. Any antibiotic, particularly a broad-spectrum agent, may play a causative role.

- (4) Tight clothing, panty hose, and bathing suits (yeast thrives in a dark, warm, moist environment).
 - (5) Undiagnosed or uncontrolled diabetes mellitus.
 - c. Another reason for a refractory monilial infection may be **compromised immune status**; with recurrent monilial vaginitis, an HIV test is indicated, along with a fasting serum glucose level.
 - d. There has been a recent **increase in the number of infections caused by non-*albicans* species**. Up to 20% of infections may be caused by organisms such as *Candida tropicalis* and *Candida glabrata*. These organisms may be resistant to standard treatment regimens.
2. **Clinical presentation.** Patients with monilial vaginitis characteristically complain of a thick, white discharge, vulvar burning, and extreme vulvar pruritus. The vulva may be red and swollen.
- a. Symptoms may recur and be most prominent just before menses or in association with intercourse.
 - b. Yeast infections may occur more frequently during pregnancy.
 - c. Patients with infections caused by *C. tropicalis* and *C. glabrata* may have an atypical presentation. Irritation may be paramount, with little discharge or pruritus.
3. **Diagnosis.** Diagnosis is made by history, physical examination, and microscopic examination of the vaginal discharge in saline and 10% KOH.
- a. On examination, excoriations of the vulva may be noticeable; the vulva and vagina may be erythematous, with patches of adherent cottage cheese-like discharge. Candidal infections of the vulva are characterized by classic **satellite lesions**.
 - b. Infection with *C. tropicalis* and *C. glabrata* may not be associated with the classic discharge; discharge may be white-gray and thin.
 - c. Vaginal pH may be normal or slightly more basic than normal (4.0 to 4.7).
 - d. Wet mount microscopic examination, along with the use of 10% KOH, reveals hyphae or pseudohyphae with budding yeast in 50% to 70% of women with yeast infections. The whiff test is negative.
 - e. Cultures are not necessary to make the diagnosis except in some cases of recurrent infections.
4. **Treatment.** Many agents are available for the treatment of vulvovaginal candidiasis. These include topical agents (azole drugs), available over the counter (OTC) or by prescription, and oral agents, which are available by prescription only.
- a. **Antifungal intravaginal agents** are administered as suppositories or creams. These drugs are available in three regimens: a single dose, 3-day course, or 7-day course. Agents include butoconazole, clotrimazole, miconazole, tioconazole, and terconazole. **OTC regimens** should be used only by women who have been diagnosed with a yeast infection in the past and are experiencing identical symptoms. Topical 7-day therapies are the only therapies recommended in pregnancy.
 - b. **Oral agents** include fluconazole and ketoconazole.
 - (1) **Fluconazole** is available as a single-dose (150 mg) treatment for uncomplicated vaginal candidiasis. For severe cases, the dose should be repeated in 72 hours. With recurrent candidiasis, doses of 100 mg, 150 mg, or 200 mg can be repeated orally on every third day (Days 1, 4, and 7) for a total of three doses.
 - (2) **Ketoconazole** is used effectively for the treatment of chronic and recurrent candidiasis; a 5% incidence of hepatotoxicity limits more widespread use. The dosing schedule is 200 mg twice a day for 5 days, then 100 to 200 mg daily for 6 months.
 - c. **Boric acid capsules intravaginally**, 600 mg for 14 days, may be effective and is usually reserved for severe or nonalbicans vulvovaginitis.
5. **Chronic recurrent yeast infections** (5% of women). In most cases, no exacerbating factor can be found; however, the following possibilities should be considered:
- a. Failure to complete a full course of therapy
 - b. **HIV infection.** Recalcitrant candidiasis may be a presenting symptom in women with HIV infection. HIV testing should be considered and offered to the patient
 - c. Chronic antibiotic therapy

- d. Infection with a resistant organism such as *C. tropicalis* or *C. glabrata*
- e. Sexual transmission from the male partner (may be considered in cases of recurrent infection)
- f. Allergic reaction to partner's semen or a vaginal spermicide
- g. Diabetes. Patients should have a fasting serum glucose level if they have recurrent infections.

C *Trichomonas vaginalis* vaginitis (trichomoniasis) is the third most common vaginitis, accounting for 25% of cases.

1. **Etiology.** The motile protozoan *T. vaginalis* is the etiologic agent. The trichomonad can be recovered from 70% to 80% of the male partners of the infected patient; therefore, *Trichomonas* vaginitis is an STD.
2. **Clinical presentation.** *Trichomonas* vaginitis is a multifocal infection involving the vaginal epithelium, Skene glands, Bartholin glands, and urethra.
 - a. Unless asked directly, 25% to 50% of women may not report symptoms.
 - b. Most women report a discharge that is described as copious, green, and frothy. The discharge may be associated with a foul odor and vulvar irritation or pruritus.
3. **Diagnosis**
 - a. **Physical examination.** Classic evidence of trichomoniasis may be seen.
 - (1) The characteristic green discharge may be evident.
 - (2) Punctuation, described classically as the "strawberry cervix," is evident in only 25% of patients.
 - b. **Laboratory tests**
 - (1) The vaginal pH is usually between 5.0 and 7.0.
 - (2) Saline wet mount of the vaginal discharge reveals **numerous leukocytes** and the highly motile, flagellated trichomonads (as many as 75% of cases). The whiff test may be positive with 10% KOH application.
 - (3) Cultures are not usually necessary to make the diagnosis. They should be obtained when the diagnosis is suspected but cannot be confirmed by wet mount examination.
 - (4) Pap smears may be positive in as many as 65% of cases. Positive Pap smears should be confirmed by wet mount examination because of the high false-positive rate.
 - (5) May coexist with bacterial vaginosis.
4. **Treatment.** Because *Trichomonas* is sexually transmitted, **both partners require therapy**; 25% of women will be reinfected if their partner does not receive treatment.
 - a. Vaginal therapy alone is ineffective because of the multiple sites of infection, and **systemic agents are necessary**.
 - b. If both partners are treated simultaneously, cure rates of 90% are achieved with treatment with **metronidazole** or **tinidazole**. Patients should be warned that a disulfiram-like reaction may occur and that they should abstain from alcohol use during treatment.
 - (1) The **preferred regimen is 2 g orally in one dose** because of ease of compliance. As many as 10% of patients may experience vomiting.
 - (2) An alternative regimen is 500 mg twice daily for 7 days.
 - c. **Recurrent cases** may be treated with metronidazole 500 mg twice daily for 7 days or tinidazole 2 g orally in a single dose. If failure occurs, treatment with a 2 g single dose of either medication for 5 days is recommended.
 - d. **Resistant cases** may require expert consultation or cultures and susceptibility testing. Because resistance is rare, other causes, such as noncompliance of the patient or partner, should be considered.
 - e. Metronidazole is **contraindicated for use during the first trimester of pregnancy**. After this time, it can be used to treat *Trichomonas* infections.
 - f. Infected patients should be screened for other STDs.

D Atrophic vaginitis

1. **Etiology.** Atrophic vaginitis, associated with decreased estradiol levels, is most often seen in postmenopausal women but also may be seen in breastfeeding women. Atrophic changes in the vulvovaginal tissues result from **estrogen withdrawal**; the normal protective thickness of the vaginal epithelium depends on estrogen stimulation.

2. Clinical presentation

- a. Without consistent and sufficient estrogen, the vaginal epithelium becomes thin; vulvar structures may atrophy.
- b. The amount of glycogen also decreases, and the pH becomes alkaline.
- c. The vagina is often pale with punctate hemorrhagic spots throughout the vaginal wall. There is an absence of superficial epithelial cells and a predominance of parabasal cells.

3. Diagnosis

- a. Atrophic vaginitis must be suspected in hypoestrogenic women who present with leukorrhea, pruritus, burning, tenderness, and dyspareunia.
- b. Physical examination of the vagina reveals atrophic, sometimes inflamed vaginal walls. A discharge may be present.
- c. Vaginal pH is usually greater than 4.5.
- d. Vaginal infection is not identified on a wet mount preparation.

4. Treatment. Topical administration of vaginal cream containing estrogen reverses symptoms and tissue changes.

- a. Symptoms respond to short-term therapy but recur on discontinuation.
- b. Changes in tissues require long-term therapy and may not be noticed until after 3 to 4 months of treatment. Proliferation and maturation of the vaginal epithelium, as well as compliance and elasticity of the vaginal wall, are restored.
- c. Therapeutic agents may be systemic or topical.
 - (1) **Hormone replacement therapy** may be given in accordance with a standard regimen.
 - (2) **Estrogen cream** is administered intravaginally every night for up to 2 weeks and then continued once or twice a week to maintain results.

E Vulvar dystrophies

1. **Etiology.** Vulvar dystrophies are dermatologic conditions of the vulvar skin of uncertain etiology. Most frequently seen in postmenopausal women, these conditions often accompany a history of chronic candidal vulvovaginitis. The dystrophies can be:
 - a. Hyperplastic when the epithelium is markedly thickened
 - b. Atrophic (lichen sclerosus et atrophicus)
 - c. A mixture of both

2. Clinical presentation

- a. With **hyperplastic dystrophy**, the most common symptom is constant pruritus. Scratching frequently exacerbates the pruritus, creating a vicious cycle.
- b. With **lichen sclerosus**, vulvar burning, pruritus, or chronic soreness associated with “vulvar dysuria” frequently occurs.

3. Diagnosis. Vulvar biopsy is ultimately necessary to make the diagnosis, but a preliminary diagnosis can be made based on **physical examination**.

- a. **Hyperplastic dystrophy** presents as thickened skin (“elephant hide”) accompanied by linear excoriations from scratching. Areas of leukoplakia may also be noted.
- b. **Lichen sclerosus** presents as extremely pale, thin skin, often with subepithelial hemorrhages. In its most severe form, painful contraction of the introitus or clitoral hood is noted. Loss of labial architecture may occur.

4. Treatment

- a. **Hyperplastic dystrophy** responds well to a 6- to 8-week trial of topical fluorinated steroid cream. Chronic therapy may be necessary on an intermittent basis.
- b. **Lichen sclerosus.** Potent fluorinated steroid creams are the treatment of choice; testosterone was used in the past but is not recommended anymore. Chronic therapy may be necessary as well.

F Traumatic vaginitis**1. Etiology.** Traumatic vaginitis is usually the result of injury or chemical irritation.

- a. In **adults**, the most common cause of injury to the vagina is a “lost” tampon.
- b. In **pediatric patients**, foreign bodies placed in the vagina serve as sources of infection or trauma (e.g., wads of paper, chewing gum, or paper clips).

- c. **Chemical irritation** can be secondary to douches, deodorants, lubricants, or topical intravaginal preparations.
- 2. **Treatment.** Vulvovaginitis resulting from foreign bodies or chemical irritants responds immediately to withdrawal of the causative agent.

G Neoplasia

- 1. **Etiology.** Malignancies can masquerade for months as vulvar lesions; thus, they are often ignored by patients or mistreated by physicians as irritations or infections.
- 2. **Diagnosis.** Patients who present with a long-term history of symptoms and treatment failures of vulvar lesions **should undergo biopsy** before receiving further therapy.
- 3. **Treatment.** Therapy appropriate for the condition described in the pathology report is indicated.

H Herpes simplex genitalis

- 1. **Etiology**
 - a. Herpes genitalis is caused by the herpes simplex virus (HSV), a member of the Herpesviridae family of viruses, which are capable of establishing latent status and causing recurrent disease.
 - b. The majority of cases of herpes genitalis are caused by HSV type 2 (HSV-2); HSV type 1 (HSV-1) is becoming more frequent as the etiologic agent in genital HSV cases.
 - c. From 60% to 85% of women with antibodies to HSV-2 have never had a recognized genital ulcer.
 - d. Transmission is through direct contact with an individual who is actively shedding virus from skin or mucous membrane lesions. Often the disease is transmitted by asymptomatic shedding of the virus.
- 2. **Clinical presentation**
 - a. **Primary infection**
 - (1) The infection is usually acquired from sexual contact, with symptoms appearing in 2 to 12 days.
 - (2) Primary infection is often associated with systemic, flu-like symptoms (e.g., malaise, myalgias, and headache). Primary symptoms may last from 2 days to 3 weeks. Symptoms may be milder and recurrences less frequent in women with antibodies to HSV-1.
 - (3) Pain and itching may precede the development of vesicular lesions, which may appear on the labia, perineum, buttocks, urethra, vagina, cervix, and bladder. Cervical involvement is seen in 70% of women with genital involvement.
 - (4) Vesicles progress to ulcers and may coalesce. Lesions are exquisitely tender. Primary lesions persist for 3 to 6 weeks and usually heal without scarring.
 - (5) Local symptoms consist of hyperesthesia, burning, itching, dysuria, and (frequently) exquisite pain and tenderness of the vulva. Vulvar pain makes intercourse unbearable and may lead to urinary retention.
 - (6) Tender inguinal lymphadenopathy may be present.
 - (7) Viral shedding may persist for 12 days.
 - (8) Complications include sacral radiculopathy with urinary or fecal retention and aseptic meningitis (rare).
 - b. **Recurrent infection**
 - (1) The dormant herpesvirus resides in the neurons of the sacral ganglia, which supply the areas of cutaneous involvement.
 - (2) Periodic asymptomatic viral shedding occurs, particularly during the first 6 months after infection.
 - (3) Recurrences are most frequent during the first year. Frequency of recurrence varies. Some patients never have another outbreak; others have frequent recurrences.
 - (4) Many women experience prodromal symptoms of itching and burning from 30 minutes to 2 days before an outbreak. Systemic symptoms usually do not occur with recurrences.
 - (5) Recurrent lesions tend to be less severe and are of shorter duration (3 to 7 days).
- 3. **Diagnosis**
 - a. When typical lesions are present, a presumptive diagnosis of herpes genitalis can be made on physical examination. Thus, **the diagnosis of herpes is a clinical diagnosis**. HSV-2 should be suspected when superficial ulcerations of the vulvovaginal tissues are identified.

- b. Viral culture is the **gold standard** by which the diagnosis of HSV infection is made. It requires 48 hours for completion. **Sensitivity** of cultures is **90% if vesicles are present, but only 30% if lesions are crusted**.
- c. Cytologic studies and direct identification methods, such as **immunofluorescence**, offer confirmatory evidence of an HSV infection but are only **50% sensitive**.
- d. **Type-specific antibodies** are available to confirm infection, especially in cases of a clinical diagnosis with negative cultures, for counseling for prognosis and recurrence risk, and in cases of an affected partner.

4. Treatment

- a. Local measures used for comfort during the acute outbreak include sitz baths and topical anesthetic creams. The area should be kept clean and dry to avoid secondary infection.
- b. Catheterization may be necessary for acute urinary retention.
- c. The **antiviral drug acyclovir**, a cyclic purine nucleoside analog, is the first antiviral drug proven to be active against herpesvirus both in vivo and in vitro. It can be applied topically or taken orally for a primary episode of HSV-2 infection. Other antiviral agents are now available.
 - (1) **Primary HSV outbreak.** Oral antiviral medications decrease the time of viral shedding, the duration of symptoms, and the time to healing in primary herpes outbreaks. Options are:
 - (a) Acyclovir 400 mg orally three times daily for 7 to 10 days
 - (b) Valacyclovir 1 g orally twice a day for 7 to 10 days
 - (c) Famciclovir 250 mg orally three times a day for 7 to 10 days
 - (d) Acyclovir 200 mg orally five times daily for 7 to 10 days
 - (2) **Recurrent HSV infection.** If oral antiviral medication is started when the recurrence begins, it also decreases duration of viral shedding, time to healing, and local symptoms.
 - (a) Acyclovir 400 mg three times daily for 3 to 5 days
 - (b) Acyclovir 800 mg three times daily for 2 days
 - (c) Valacyclovir 500 mg orally twice daily for 3 days
 - (d) Famciclovir 125 mg orally twice daily for 3 to 5 days
 - (3) **Suppressive therapy.** Studies have shown that oral acyclovir decreases the frequency of recurrences by as much as 75%. Providers should annually discuss the discontinuation of therapy, and the frequency of recurrences is documented. If greater than six recurrences are documented, treatment is restarted as indicated.
 - (a) Acyclovir 400 mg twice daily. Suppressive therapy has been approved for up to 6 years.
 - (b) Famciclovir 250 mg twice daily.
 - (c) Valacyclovir 500 mg to 1 g once daily. Valacyclovir therapy for suppression has been approved for up to 1 year.



Study Questions for Chapter 35

Directions: Match each word or statement below with the most specific anatomic site. Each answer may be used once, more than once, or not at all.

- ☐ A Labia majora
- ☐ B Labia minora
- ☐ C Clitoris
- ☐ D Vestibule
- ☐ E Prepuce
- ☐ F Bartholin gland
- ☐ G Skene gland
- ☐ H Pudendal
- ☐ I Ilioinguinal
- ☐ J Posterior femoral cutaneous
- ☐ K Internal pudendal
- ☐ L Cervical

1. Embryologic homolog in the male is the scrotum
2. Embryologic homolog in the male is the Cowper gland(s)
3. Paraurethral gland
4. Major nerve supplying innervation to the vulva
5. Major blood supply to the vulva

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

6. A 21-year-old woman, gravida 2, para 1, at 20 weeks of gestation, presents to your office and reports increasing gray vaginal discharge that has an odor. A wet mount reveals leukocytes and motile trichomonads. She denies pruritus. She does not have any significant medical history or allergies to medication. The next step in management of this patient is:

- ☐ A Oral metronidazole, with partner treatment
- ☐ B Vaginal metronidazole
- ☐ C Oral azithromycin, with partner treatment
- ☐ D Vaginal clindamycin, with partner treatment
- ☐ E Oral fluconazole

7. A 20-year-old student presents to your office reporting four days of the presence of painful vulvar lesions and difficulty with urination. Examination reveals multiple small, coalescent ulcerations on the labia majora and tender, bilateral inguinal lymphadenopathy. She admits to recent unprotected intercourse with a new partner. What is the next step in management of this patient?

- ☐ A Oral fluconazole
- ☐ B Viral culture, STD screening and Valacyclovir 1 g twice daily for 7 to 10 days
- ☐ C Famcyclovir 250 mg twice daily
- ☐ D Acyclovir 400 mg three times daily for 3 days
- ☐ E Viral culture, STD screening and Valacyclovir 500 mg twice daily for 3 days

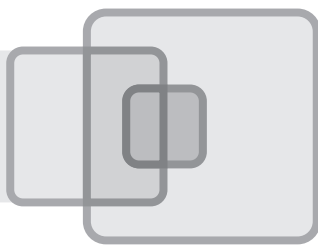
8. A 29-year-old obese female with hepatitis C presents complaining of her third yeast infection in the past month. You recommend:

- ☐ A Fasting glucose
- ☐ B HSV testing
- ☐ C Wet mount to look for characteristic clue cells
- ☐ D Ketoconazole therapy
- ☐ E Treatment with metronidazole



Answers and Explanations

1. **A** [II A 1 d2], 2. **F** [II A 1 h2], 3. **G** [II A 1 i], 4. **H** [II A 2 a], 5. **K** [II A 3]. The embryologic homolog of the labia majora in the male is the scrotum. The embryologic homolog of the Bartholin glands in the male is the Cowper glands.
6. **The answer is A** [VI C 4a,b]. Oral metronidazole is the method of treatment; vaginal therapy alone may be ineffective. Partner treatment is indicated to ensure cure, due to a 25% reinfection rate with an untreated partner. Vaginal metronidazole and clindamycin are effective treatments for bacterial vaginosis. Azithromycin may be used for treatment of chlamydia. Oral fluconazole is a treatment for candidal infections of the vulva and vagina.
7. **The answer is B** [VI H 2, 4c]. A primary HSV outbreak is described. Due to recent unprotected intercourse and the transmission of HSV, complete screening for other sexually transmitted infections is offered. Duration of treatment for a primary infection is 7 to 10 days with 2- to 5-day regimens for recurrent HSV infections.
8. **The answer is A** [VI B 5]. Fasting glucose is indicated for recurrent yeast infection to evaluate for the presence of diabetes. Other testing that is indicated is HIV testing, not HSV, as recurrent yeast infections are associated with HIV infection. Wet mount would be expected to reveal hyphae, not clue cells which are seen with BV. Ketoconazole therapy would not be the first choice as this patient has hepatitis C and liver toxicity is associated with ketoconazole. Metronidazole would not treat a yeast infection.



Disorders of the Pelvic Floor

LILY ARYA • SAYA SEGAL

I

INTRODUCTION

A Epidemiology

1. Urinary incontinence affects women five times more often than men.
2. From 10% to 25% of women 25 to 64 years of age and as many as 40% of women older than 65 years of age suffer from some form of urinary incontinence.
3. As many as 50% of all parous women have pelvic support defects, and 10% to 20% seek care for pelvic organ prolapse (POP).
4. In the United States, women have a lifetime risk of urinary incontinence or POP that requires surgical treatment of approximately 11%.
5. The true prevalence of fecal incontinence is unknown, but the disorder is estimated to affect as many as 10% of women older than 64 years of age.
6. Thirty percent of women with urinary incontinence also have fecal incontinence.

B Anatomy of the pelvic floor (Fig. 36–1) The pelvic organs rest on the pelvic floor muscles and are held in place with the help of the endopelvic fascia.

1. The pelvic floor is made up of the **levator ani** and coccygeus muscles. The levator ani has three parts, including the puborectalis and pubococcygeus (also referred to as the pubovisceral muscle) and iliococcygeus muscles.
 - a. These muscles, which create a hammock-like sling between the pubis and coccyx, are attached laterally along the pelvic sidewalls.
 - b. The levator ani muscle is tonically contracted, providing a firm shelf posteriorly to support the pelvic contents and aiding with urinary and fecal continence.
2. **Endopelvic fascia** is a loose network of connective tissue, small vessels, lymphatics, and nerves, which surrounds and supports the pelvic organs and the vagina. Thickenings of the endopelvic fascia are known as ligaments (e.g., the uterosacral and cardinal ligaments, rectovaginal and vesicovaginal fascia).
3. The **vagina** is attached at three levels. The apex is supported by the cardinal and uterosacral ligaments. The midvagina is supported by the attachment of the vagina to the levator ani at the arcus tendineus fascia pelvis (white line). The lower vagina is supported by its attachment to the perineal membrane and the perineal body. Normal vaginal attachments help to keep the pelvic organs (i.e., the uterus, bladder, and rectum) in place.

C Innervation of the pelvic floor and its functions

1. The levator ani is innervated by the nerve to the levator ani (S3 to S5). This muscle group is tonically stimulated to contract, providing constant support to the pelvic organs.
2. Bladder filling and voiding functions are controlled by closely coordinated autonomic and somatic pathways.
 - a. **Autonomic nervous system**
 - (1) **Sympathetic** (thoracolumbar) nerves promote urine storage by **relaxing the bladder (detrusor) muscle** and contracting smooth muscle in the bladder neck and urethra. These nerves are inhibited during voiding.

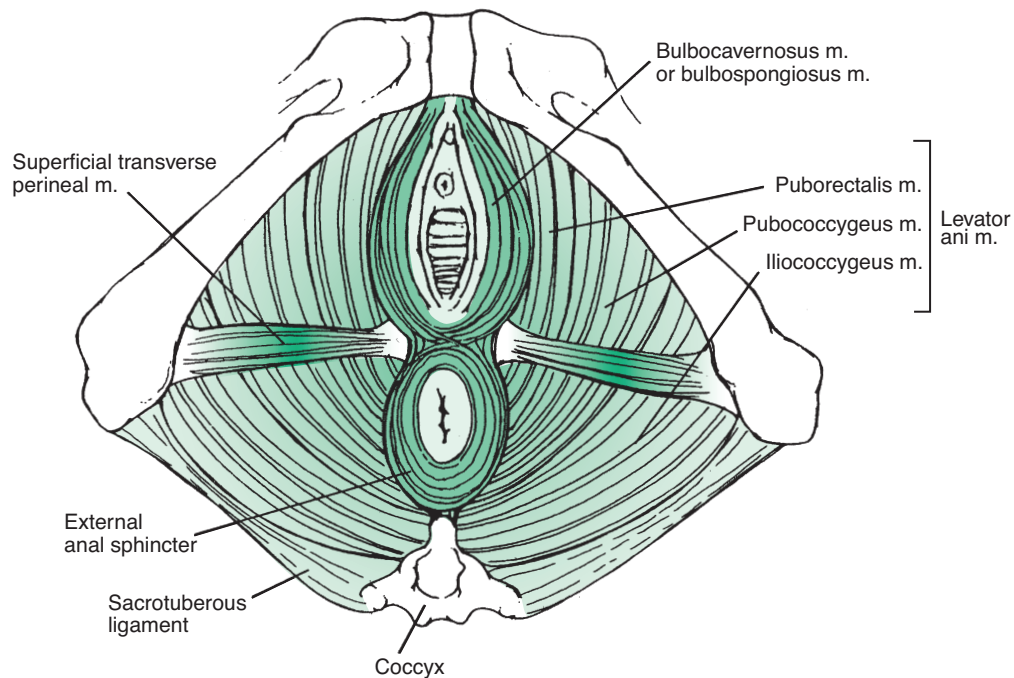


FIGURE 36-1 Levator ani muscles from below. The levator ani has several parts, including the pubovisceral and iliococcygeus muscles. m., muscle.

- (2) **Parasympathetic** (sacral) nerves cause the detrusor muscle to contract. They are stimulated during micturition.
- b. The **somatic nervous system** controls the striated external urethral sphincter and levator ani muscle through the pudendal nerve and the sacral nerve roots (S3 to S5). Inhibition of these nerves causes relaxation of the bladder outlet and pelvic floor, which must occur during voiding.
- c. The **central nervous system** (CNS) provides voluntary control and modification of micturition and defecation reflexes.

II

PELVIC ORGAN PROLAPSE

Such prolapse or protrusion of pelvic structures into the vaginal canal results from weakening or damage to pelvic support structures.

A Risk factors

1. Vaginal childbirth may damage or weaken pelvic support structures. This damage may be direct injury to the muscle and fascia of the pelvis or indirect weakness of the muscles caused by neurologic injury.
2. Obesity, chronic cough, and chronic constipation may cause increased intra-abdominal pressures, increasing the risk of POP.
3. Increasing age and menopause are associated with an increased risk of POP.
4. A genetic predisposition for POP may exist in some women.

B Terminology

1. **Cystocele** is protrusion of the bladder behind the anterior vaginal wall. This represents failure of support at the midvagina anteriorly.
2. **Uterine prolapse** is descent of the uterus into the lower part of the vagina or through the vaginal opening.
3. **Vaginal vault prolapse** is descent of the vaginal apex after hysterectomy. Uterine prolapse and vaginal prolapse represent failure of apical support of the vagina.
4. **Enterocele** is protrusion of small bowel behind the upper vaginal wall into the vaginal canal.

TABLE 36-1 Stages of Pelvic Organ Prolapse (Most Distal Portion of Prolapse*)

Stage	Pelvic position
0	-3
1	-2
2	-1 to +1
3	≥ +2
4	Vaginal eversion

*Most distal portion of the prolapse when examined under maximal strain (cm).

5. **Rectocele** is protrusion of the rectum behind the posterior vaginal wall. This represents failure of the midvaginal support posteriorly.

6. **Relaxed or widened vaginal outlet.** This represents failure of support of the lower vagina.

C Symptoms Mild forms of POP are often asymptomatic. Advanced forms of POP may cause difficulty with urination or defecation. Associated symptoms may include:

1. **Bulge of tissue** protruding through the vaginal opening
2. Pelvic or vaginal **pressure**, especially after prolonged standing
3. Dyspareunia

D Evaluation

1. Prolapse is diagnosed on **pelvic examination**, performed in the lithotomy and standing positions.
2. The severity of prolapse may be classified according to systems that describe the location and severity of POP (Table 36-1).
 - a. **Pelvic Organ Prolapse Quantification (POP-Q)** (Fig. 36-2)
 - b. Halfway system (Table 36-2)

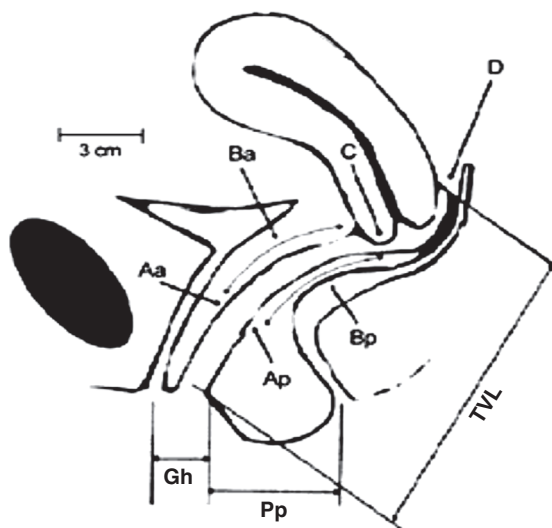


FIGURE 36-2 Pelvic organ prolapse quantification system. **Aa**, anterior vaginal wall site 3 cm proximal to the external urethral meatus (ranges from -3 to +3 cm) measured from the hymen* with maximal strain or valsalva; **Ba**, anterior vaginal wall site representing the most distal aspect of the anterior vaginal wall prolapse (cm) in relation to the hymen* with maximal strain or valsalva; **Ap**, posterior vaginal wall site 3 cm proximal to the hymen (ranges from -3 to +3 cm) measured from the hymen* with maximal strain or valsalva; **p**, posterior vaginal wall site representing the most distal aspect of the posterior vaginal wall prolapse in relation to the hymen* with maximal strain or valsalva; **C**, cervix or vaginal cuff in women after hysterectomy measured in cm in relation to the hymen* with maximal strain or valsalva; **D**, posterior fornix (in women with a cervix) measured in cm in relation to the hymen* with maximal strain or valsalva; **Gh**, genital hiatus measured in cm from the middle of the urethral meatus to the posterior hymen* at rest; **Pp**, perineal body measured in cm from the poster margin of gh to midanal opening at rest; **TVL**, total vaginal length in cm measured from the posterior fornix or vaginal cuff to the hymen at rest.

*Proximal to the hymen is "+n," at the hymen is "0," and distal to the hymen is "-n."

TABLE 36–2 The Halfway Grading System for Pelvic Organ Prolapse*

Grade	Level of Prolapse
1	No prolapse
2	Descent halfway to the hymen
3	Descent to the hymen
4	Descent halfway past the hymen
5	Maximum possible descent for each site

*Descent of the most dependent portion of the prolapse is graded during maximal straining.

E Treatment Asymptomatic POP does not require treatment.

1. **Pelvic floor muscle (Kegel) exercises** may improve symptoms caused by mild forms of prolapse by strengthening the levator ani muscles.
2. **Pessaries** are removable devices placed in the vagina that support prolapse.
3. **Surgery** for POP aims to relieve symptoms and to restore normal anatomic relationships. The surgical procedure and approach (abdominal or vaginal) is tailored to the patient and to the particular type of POP present.
 - a. **Hysterectomy** for uterine prolapse
 - b. **Anterior repair, paravaginal repair** for cystocele
 - c. **Posterior repair** for rectocele
 - d. **Enterocoele repair**
 - e. **Vaginal vault suspension (sacrospinous ligament suspension, uterosacral vault suspension, abdominal sacrocolpopexy)**
 - f. **Perineorrhaphy** for relaxed vaginal outlet.

III

URINARY INCONTINENCE

A Types

1. **Stress urinary incontinence (SUI)** is the loss of urine that occurs with increased abdominal pressure, such as coughing or straining. SUI is the result of loss of **anatomic support of the urethrovesical junction or urethra**. It most commonly occurs following pelvic floor muscle and nerve damage that resulted from pregnancy and childbirth.
 - a. **Urethral hypermobility** is the most common form of SUI and usually follows child birth injury to urethral support. The SUI occurs because the urethra can no longer be compressed against the vagina during raised intra-abdominal pressure.
 - b. **Intrinsic sphincter deficiency** is less common and is caused by a weakened urethral sphincter. Severe SUI develops even with minimal exertion. Risk factors are scarring from prior anti-incontinence surgery and aging.
2. **Urge incontinence** is defined by the symptom of urine loss that occurs when the patient experiences urgency, or a strong desire to void. This type of incontinence is often accompanied by symptoms of urinary frequency, urgency, and nocturia. Urge incontinence includes the following subtypes:
 - a. **Detrusor overactivity (DO)** (previously called detrusor instability), or overactive bladder, is caused by involuntary detrusor contractions. Its cause is usually unknown.
 - b. **Neurogenic DO** is involuntary detrusor contractions associated with a neurologic disorder (e.g., stroke, spinal cord injury, or multiple sclerosis). It is a common cause of incontinence in elderly and institutionalized women.
3. **Overflow incontinence** occurs because of underactivity of the detrusor muscle. This form of incontinence is associated with retention of urine. The bladder does not empty completely, and “dribbling” of urine occurs.
4. **Extraurethral sources of urine** include genitourinary fistulas, which result from obstetric injuries or follow pelvic surgery or radiation. These typically cause continuous leaking of urine.

B Evaluation

1. A **detailed history** is essential and should include:
 - a. **Urinary symptoms**, including the presence of voiding frequency, nocturia, urgency, precipitating events, and frequency of loss. A voiding diary allows the patient to document voiding frequency and incontinence episodes during a specific period
 - b. Previous urologic surgery
 - c. Obstetric history, including parity, birth weights, mode of delivery, and lacerations
 - d. CNS or spinal cord disorders
 - e. Use of medications, including diuretics, antihypertensives, caffeine, alcohol, anticholinergics, decongestants, nicotine, and psychotropics
 - f. Presence of other medical disorders (e.g., diabetes, hypertension, or hematuria)
2. **Physical examination** may detect:
 - a. Exacerbating conditions, such as chronic obstructive pulmonary disease, obesity, or intra-abdominal mass
 - b. Hypermobility of the urethra
 - c. POP
 - d. Neurologic disorders
3. **Diagnostic tests**
 - a. A midstream urine specimen is collected for **urinalysis** or **culture and sensitivity**. Infection may aggravate urinary incontinence.
 - b. **Postvoid residual urine volume** should be measured (by ultrasound or catheterization) after the patient has voided. Typically, the postvoid residual urine volume is between 50 to 200 mL.
 - c. The **Q-tip test** is an indirect measure of the urethral axis. A Q-tip is inserted into the urethra with the patient in the lithotomy position. If the Q-tip moves more than 30 degrees from the horizontal with straining, **urethral hypermobility** is present.
 - d. **Urodynamic testing**, including a cystometrogram and voiding studies, may be useful for demonstrating the type of incontinence present. These tests measure pressures within the bladder and abdomen during bladder filling and emptying. Multichannel urodynamic testing is indicated for complex cases of urinary incontinence such as mixed incontinence (presence of two or more kinds of incontinence in the same patient) or in patients with incontinence and retention of urine.
4. **Cystoscopy** is performed in some patients to examine the bladder and urethral mucosa for abnormalities such as diverticula or neoplasms.

C Treatment Therapy depends on the underlying diagnosis.

1. **Treatment of exacerbating factors** such as excess weight, chronic cough, or constipation may improve SUI.
2. **Pelvic muscle rehabilitation** may be helpful for both SUI and DO.
 - a. Kegel exercises
 - b. Vaginal cones
 - c. Biofeedback
 - d. Electrical stimulation
3. **Pessaries**, other intravaginal devices, and urethral plugs and inserts are useful conservative therapies for SUI.
4. **Drug therapy** is the mainstay of treatment for DO but is of limited value in treating SUI.
 - a. **Anticholinergic agents** (oxybutynin and tolterodine) are highly effective and are the most commonly prescribed treatments for DO. However, they cause side effects, such as dry mouth and constipation, in about 25% of patients.
 - b. α -Adrenergic stimulating agents (e.g., pseudoephedrine, imipramine) increase smooth muscle contraction in the urethral sphincter and may decrease SUI symptoms.
 - c. **Estrogens** (systemic or vaginal) improve irritative bladder symptoms such as urgency and dysuria in postmenopausal women but do not significantly improve urinary leakage. Hormone replacement therapy does not reduce the incidence of urinary symptoms in postmenopausal women.

5. **Surgery** is extremely effective in the treatment of SUI. It is rarely helpful for DO and is generally reserved only for intractable cases.
 - a. **Injection of bulking agents** around the urethra is a minimally invasive procedure to treat SUI resulting from intrinsic sphincter deficiency. Collagen, the bulking agent currently used most commonly, provides a temporary (3 to 12 months) cure or improvement rates ranging from 50% to 70%. They are generally indicated for patients unable to tolerate major surgery.
 - b. **Retropubic urethropexy** elevates the urethra and bladder neck by fixing the paraurethral connective tissues to the pubis. The most common type of retropubic operation performed is the **Burch** procedure, which suspends the vaginal fascia lateral to the urethra to the iliopectineal line (Cooper ligament). Burch procedures are most successful in patients who have SUI associated with urethral hypermobility, resulting in long-term cure rates of 75% to 90%. Postoperative complications are uncommon but may include urinary retention and new DO. The procedures may be performed via an abdominal incision or laparoscopically.
 - c. **Transvaginal needle procedures** stabilize the bladder neck by anchoring vaginal tissue to the rectus fascia or symphysis pubis. These procedures have lower long-term cure rates than retropubic operations and midurethral slings and are now not generally performed.
 - d. **Urethral sling procedures**, which place various biologic and synthetic materials under the urethra, appear to affect treatment by partially obstructing the urethra during times of increased intra-abdominal pressure. Midurethral sling procedures differ according to the type of material and the sling fixation points used; however, they all have high cure rates (80% to 90%). Sling procedures are more effective than retropubic operations in patients with **intrinsic sphincter deficiency**. Complications of sling procedures may include infection and ulceration (especially with the use of synthetic grafts) and **urinary retention**.

IV

FECAL INCONTINENCE

The involuntary loss of stool or gas is a socially embarrassing disorder. Symptoms of fecal incontinence are often not reported to physicians.

A Pathophysiology

1. Fecal continence depends on stool consistency and volume, colonic transit time, rectal compliance, and innervation and function of the anal sphincter and pelvic floor.
2. Gastrointestinal and neurologic disorders may result in fecal incontinence.
3. Obstetric injuries to the pelvic floor, as well as denervation injuries related to childbirth or chronic straining, are the most common cause of fecal incontinence in women.

B Symptoms

1. Fecal urgency
2. Incontinence of flatus
3. Incontinence of stool

C Evaluation A detailed history and examination, including a vaginal and rectal examination, are essential. Useful tests for determining the etiology of fecal incontinence may include anal ultrasound, anal manometry, and pelvic floor nerve conductance studies.

D Treatment Therapy may include behavioral modification, pharmacologic agents, biofeedback, and surgery.



Study Question for Chapter 36

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A 60-year-old woman, gravida 5, para 4, spontaneous abortions 1, has been treated with vaginal estrogen therapy, various pelvic muscle rehabilitation therapies, and pessaries for symptoms of pelvic prolapse without incontinence for the past 2 years. She desires definitive therapy. She has no past medical history other than hypertension, for which she takes hydrochlorothiazide. All of her children were delivered vaginally. On pelvic examination, vaginal mucosa is pink and moist. The anterior vaginal wall prolapses up to the hymenal ring on Valsalva. When the anterior vagina is supported with half of the speculum, the uterus and cervix prolapse past the hymenal ring as well. There is no stress incontinence when the urethrovesical junction is supported and the cystocele reduced. The uterus is normal in size, contour, and consistency. The sacral neurologic examination is unremarkable. A urine culture is sent. The next best step in management of this patient is:

- ☐ A Electrical stimulation of pelvic musculature
- ☐ B Hysterectomy
- ☐ C Vaginal hysterectomy, uterosacral vault suspension, and anterior repair
- ☐ D Vaginal hysterectomy, anterior repair, and midurethral sling
- ☐ E Burch retropubic urethropexy and anterior repair

2. A 32-year-old woman, gravida 3, para 3, just delivered a viable female infant weighing 4,000 g via cesarean section for nonreassuring fetal heart rate pattern. She received intrathecal (spinal) anesthetic and narcotic for pain relief during the procedure. Her Foley catheter is left in place for several hours after the cesarean section. This will prevent:

- ☐ A Stress incontinence
- ☐ B Urge incontinence
- ☐ C Overflow incontinence
- ☐ D Bypass incontinence
- ☐ E Postoperative urinary tract infection

3. A 56-year-old woman, gravida 2, para 2, who reports leaking urine when she coughs and exercises, is diagnosed with genuine SUI. Her examination is significant for a Q-tip test 45 degrees from the horizontal. A regimen of Kegel exercises and a pessary do not improve her symptoms, and she desires more definitive treatment. The next best step in surgical management is

- ☐ A Vaginal hysterectomy
- ☐ B Anterior repair
- ☐ C Needle suspension
- ☐ D Periurethral injection
- ☐ E Midurethral sling

4. A 67-year-old woman, gravida 3, para 3, presents to your office reporting incontinence. She tells you that she voids almost 20 times during the day and has several episodes of nocturia. She says she feels like voiding two times an hour and that when she makes it to the bathroom, only small amounts of urine are voided. Her past medical history is remarkable for mild asthma, for which she takes albuterol. Her previous gynecologist also placed her on estrogen vaginal cream. She had a cholecystectomy 20 years ago. Her BP = 130/80 mm Hg, P = 80 bpm, height = 5 feet 4 inches, weight = 230 lb. On physical examination you notice pink, moist vaginal epithelium with mild cystocele and well-supported proximal urethra. The next best step in management of this patient is:

- ☐ A Urinalysis
- ☐ B Tolterodine
- ☐ C Pseudoephedrine
- ☐ D Pessary
- ☐ E Suburethral midurethral sling

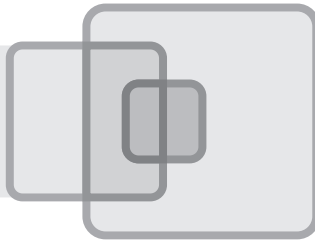
5. A 55-year-old Caucasian woman, gravida 3, para 3, who delivered all of her children by scheduled cesarean sections (prior to initiation of labor), has mild POP. She had her last period 3 years ago and since that time has been on hormone replacement therapy for treatment of intractable hot flushes and vaginal dryness. She has no chronic medical problems but is on antibiotic therapy for acute bronchitis. Her family history is significant for osteoporosis in two sisters and SUI in her mother. The strongest risk factor for POP in this patient is:

- ☐ A Parity
- ☐ B Age
- ☐ C Hormone status
- ☐ D Genetic
- ☐ E Cough



Answers and Explanations

1. **The answer is C** [II E 3]. The patient has uterine prolapse and cystocele, and conservative treatment (pelvic muscle rehab, pessary, and estrogen) has failed. Therefore, the next best treatment is surgical. Cystocele can be treated with an anterior repair, but this does not address her uterine prolapse. Uterine prolapse can be cured with a hysterectomy and suspension of the vagina vault either by a vaginal approach or abdominal approach. Therefore, the patient needs a hysterectomy with a uterosacral vault suspension to support the vaginal apex. A midurethral sling is unnecessary for this patient because, in the clinical scenario, “there is no stress incontinence when the urethrovesical junction is supported and the cystocele reduced.” Burch retropubic urethropexy is also for treatment of SUI. Electrical stimulation is a form of pelvic muscle rehabilitation that has been tried and failed.
2. **The answer is C** [III A 3]. Intrathecal anesthetics and narcotics block nerve impulses to and from the bladder. When the bladder becomes distended with urine, the afferent impulses cannot be transmitted, and therefore the bladder detrusor muscle is underactive. This results in overdistension of the bladder, urinary retention, and overflow incontinence. The risk of urinary tract infection is increased with placement of a Foley catheter.
3. **The answer is E** [III C 4,5]. SUI is effectively treated by surgery after conservative measures have failed. Midurethral slings are a minimally invasive procedure that has been used in the United States since the late 1990s and have higher cure rates and less urinary retention compared to the Burch procedure. Needle suspension procedures also have lower cure rates than midurethral slings. Periurethral bulking agents are preferred in cases of SUI caused by intrinsic sphincter deficiency. Vaginal hysterectomies do not treat SUI.
4. **The answer is A** [III B 3a]. Although the clinical scenario is almost definitely urge incontinence, you must rule out urinary tract infection (UTI) because it may mimic symptoms of urgency. Once UTI is ruled out, you may begin therapy with tolterodine or oxybutynin. Pessary and midurethral slings are not as useful for DO as they are for stress incontinence.
5. **The answer is D** [II A]. The cause of POP is multifactorial. Genetics determine the subtype and density of collagen and connective tissue that a person inherits. Parity is not a risk factor in this patient because she has not had any vaginal deliveries and all of her cesarean sections were performed prior to initiation of labor. Coughing as a result of acute bronchitis is not a risk factor for POP. This patient is only 55 years old; therefore, her age is not as large a determinant of her pelvic relaxation as in a woman who is 85 years old. This patient has been on hormone replacement since menopause; therefore, the tissues derived from the urogenital sinus have been stimulated adequately and continuously with estrogen.



Menopause

MAUREEN KELLY

I

DEFINITIONS

A Menopause

1. **Menopause** is the **permanent cessation of menses occurring as a result of loss of ovarian hormone production**. It is retrospectively defined as the absence of menses for 1 year due to hypergonadotropic hypoenestrogenism.
2. The median age of naturally occurring menopause is 51.4 years. Ninety percent of women experience menopause between the ages of 45 to 55 years. Although the average age at which menopause occurs is stable worldwide, it is influenced in individuals by genetic predisposition and any events that reduce the ovarian follicle pool.
3. **Premature menopause** or **premature ovarian failure** is defined as the permanent cessation of menses occurring before 40 years of age as a result of loss of ovarian function.
4. **Menopause** can be spontaneous or induced by surgery, chemotherapy, radiation, or other exogenous influences.

B Perimenopause

1. The **perimenopause** is the time prior to menopause which is marked by hormonal changes in the hypothalamic–pituitary–ovarian axis. Clinically, a woman may notice menstrual cycle changes and symptoms such as hot flushes and night sweats. Physiologically, there are wide fluctuations in follicle-stimulating hormone (FSH) secretion and estradiol production.
2. On average, the perimenopause occurs for 4 years prior to menopause. Although hormonal changes occur, not all women will experience changes in their menstrual pattern. In fact, approximately 10% of women maintain regular menses up to the point of menopause.

- C Postmenopause** begins with the final menstrual period (FMP) and continues for the duration of the woman's life.

II

PHYSIOLOGY OF PERIMENOPAUSE

- A Ovarian function** The ovary is responsible for hormonal production and ovulation. These two functions are altered during the perimenopause transition and ultimately cease at menopause.

1. **The number of oocytes, 2 million at birth, decreases to 400,000 at puberty through atresia and ovulation. The rate of atresia increases at the age of 35 or when there are approximately 25,000 oocytes remaining.** Approximately 1,000 oocytes remain at the age of 51, the average age of menopause.
2. Ovulatory cycles diminish and, although fertility is reduced, **pregnancy can occur. The percentage of normal eggs released is extremely low, explaining the decline in fecundity and increases in miscarriage and aneuploidy in the perimenopausal age group.**

B Endocrinology

1. **Inhibin** is produced by the ovary and exerts a negative feedback on secretion of FSH from the pituitary. Levels of inhibin B are reduced with ovarian aging leading to an overall increase in FSH levels.

2. **Luteinizing hormone (LH)** is not under the negative feedback of inhibin, and LH levels are not affected by the loss of inhibin production. The increase in FSH levels precedes elevation of LH by 10 years.
3. **Estradiol** levels are normal or higher than those seen in normal ovulatory cycles as a result of the elevated FSH levels.
4. **Progesterone** levels reflect the ovulatory status of the specific cycle and the phase at which it is drawn within the cycle.
5. **Androgen** levels are unchanged or slightly decreased in perimenopause.

C Menstrual cycles Changes in the menstrual cycle reflect changes in ovarian function and circulating levels of ovarian steroids and pituitary gonadotropins.

1. **Changes in menstrual cycle regularity** occur as a woman enters the perimenopausal transition. One of the first changes noted is a shorter cycle length, reflecting a shorter follicular phase. Luteal phase is generally constant, between 11 and 14 days.
2. Cycles are typically ovulatory in the early perimenopausal phase, albeit with a shortened follicular phase. The latter occurs as a result of the elevated FSH levels.
3. **Anovulatory cycles** and **prolonged cycles** become more frequent as menopause approaches, resulting in oligomenorrhea.
4. **Irregular anovulatory cycles** in perimenopause place the woman at risk for endometrial hyperplasia and should be evaluated with endometrial sampling.

III

PHYSIOLOGY OF MENOPAUSE

A Ovarian function Follicular reserve is depleted resulting in amenorrhea.

1. **Few follicular units remain in the postmenopausal ovary**, and those present no longer respond despite stimulation by elevated gonadotropins.
 - a. **FSH receptors** are absent on a cellular level.
 - b. **Estradiol** production by the ovary depends on FSH stimulation of follicles, and is negligible in the postmenopausal ovary. The greatest decline in estradiol levels are in the first year after the FMP and decrease more gradually in subsequent years.
 - c. **Estradiol and inhibin levels are too low to exert a negative feedback on FSH.**
 - d. **Estrone**, a less potent estrogen than estradiol, is the predominant estrogen in menopause. It is produced in small amounts in the ovary and peripheral tissues. It is derived from metabolism of estradiol and from peripheral aromatization of androstenedione in adipose and muscle tissue.
2. **Ovarian stromal tissue** continues to produce androgenic steroid hormones for several years after the menopause.
 - a. Ovarian stromal cells possess LH receptors and respond with the production of **ovarian androgens** (e.g., androstenedione, testosterone, and dehydroepiandrosterone [DHEA]).
 - b. **Androstenedione** and **DHEA** production continues at a decreased rate compared to premenopausal output. **Testosterone** production remains stable or may be slightly increased.
3. Once the diagnosis of menopause is made on the basis of 1 year of amenorrhea and FSH levels are persistently greater than 30 mIU/mL, contraception is not necessary.

B Endocrinology

1. **FSH levels** are elevated 10 to 20 times above premenopausal levels, reaching a plateau 1 to 3 years after menopause, after which there is a gradual decline. This reflects loss of the negative feedback effects of both inhibin and estradiol. FSH levels never return to the premenopausal range, even with estrogen replacement therapy, reflecting the influence of inhibin.
2. **LH levels** rise two- to three-fold after menopause, reaching a plateau in 1 to 3 years, after which there is a gradual decline. This reflects the loss of the negative feedback effect of estradiol.
3. Although **ovarian estrogen production** is negligible after menopause, there is individual variation in circulating estrogen levels because of peripheral conversion of androgenic precursors to estrone.

- a. **Androgens**, which serve as precursors for estrone, continue to be produced by the postmenopausal ovary and the adrenal gland.
- b. **Aromatase enzymes** that convert androgens to estrone primarily (and estradiol to a lesser degree) are present in peripheral tissues but are **predominantly present in adipose tissue**. **Obesity** can lead to a state of relative estrogen excess.
- 4. **Peripheral testosterone levels** are decreased during the postmenopausal stage. Circulating testosterone levels are the net result of androstenedione and testosterone production by both the adrenal gland and the ovary.
 - a. Testosterone and androstenedione production by the adrenal gland fall with age.
 - b. Testosterone production by the ovaries does not decrease for several years after menopause.
 - c. Androstenedione production by the ovary is markedly reduced after menopause.
- 5. **DHEA levels** are reduced after menopause. However, DHEA sulfate levels, which reflect adrenal gland activity, are unchanged.
- 6. **Sex hormone-binding globulin (SHBG)** is decreased by 40% in association with the decrease of estradiol. As a result of the decrease in SHBG, the ratio of free androgen to SHBG is increased, allowing more circulating unbound testosterone.

C **Premature menopause** or **premature ovarian failure** is the cessation of menses in a woman **younger than 40 years of age**. Premature ovarian failure can be transient. When it is permanent, the ovaries fail to respond to either endogenous or exogenous gonadotropins.

- 1. The frequency of premature ovarian failure is 0.3%. This is the diagnosis in 5% to 10% of women presenting with secondary amenorrhea.
- 2. Most women with premature menopause undergo premature oocyte atresia and follicular depletion. This results from one of three mechanisms:
 - a. Decreased initial germ cell number at birth
 - b. Accelerated oocyte atresia after birth
 - c. Postnatal germ cell destruction or removal. Examples of this include surgical removal of ovary, chemotherapy, and radiation
- 3. Etiologies of premature ovarian failure and hypergonadotropic amenorrhea are diverse and fall under one of the following categories (see Chapter 22):
 - a. Genetic and cytogenetic abnormalities
 - b. Enzymatic defects
 - c. Metabolic defects
 - d. Physical insults and iatrogenic causes
 - e. Autoimmune disturbances
 - f. Abnormal gonadotropin structure or function
 - g. Idiopathic

IV

CLINICAL MANIFESTATIONS OF PERIMENOPAUSE

A **Manifestations of estrogen excess** During perimenopause, some women present with evidence of estrogen excess rather than deficiency, due to a transient increase from increased FSH levels.

- 1. **Abnormal uterine bleeding (AUB)** is bleeding that is excessive in amount, duration, and frequency. It can occur due to prolonged exposure of the uterine lining to estrogen stimulation unopposed by progesterone. It may also be due to structural or systemic abnormalities. AUB without known structural or endocrine causes is called **dysfunctional uterine bleeding (DUB)**.
 - a. **Anovulatory cycles**, common to the perimenopausal transition, lead to unopposed estrogen stimulation of the endometrial lining. This in turn can cause dyssynchronous shedding of the endometrium.
 - b. Increased endogenous estrogen can also be caused by **increased peripheral conversion of androgen** precursors to **estrone** and estradiol. This is most frequently seen in obese perimenopausal women.

- c. There are many other **causes of AUB not related to sex hormone fluctuation**. Examples are endometrial polyps, fibroids, pregnancy, infection, coagulopathy, disorders of thyroid or prolactin regulation, chronic illness, and exogenous medications.
2. **Endometrial neoplasia**
 - a. Prolonged unopposed estrogen stimulation of the endometrial lining may lead to excessive endometrial proliferation and subsequent endometrial pathology. This often presents as vaginal bleeding or AUB.
 - b. AUB that occurs either in a woman older than 40 years of age or in a younger woman with risk factors (history of chronic anovulation or unopposed estrogen, prolonged bleeding, obesity) must be evaluated with pelvic examination, pregnancy test, laboratory work as indicated by history, and endometrial sampling to rule out disease. **Endometrial biopsy, with or without pelvic ultrasonography**, is usually sufficient. **Dilation and curettage (D&C) with hysteroscopy and sonohysterography** are alternatives for diagnostic testing.
 - c. **Simple endometrial hyperplasia** has low risk (3% to 5%) of progression to endometrial carcinoma and can be treated medically.
 - d. **Complex endometrial hyperplasia without atypia** is a more advanced type of hyperplasia, with a 10% risk of progressing to endometrial carcinoma. Complex hyperplasia may also be treated medically, followed up with posttreatment tissue sampling.
 - e. **Complex endometrial hyperplasia with atypia** is associated with an increased risk of an associated endometrial carcinoma. Because of an approximately 25% risk of progression to endometrial carcinoma, hysterectomy is the treatment of choice for this condition. However, if medical management is elected, hysteroscopy with D&C is necessary first to rule out the coexistence of endometrial cancer.
 - f. **Endometrial cancer** should be suspected in all perimenopausal women who present with abnormal bleeding. As much as 10% of postmenopausal bleeding is secondary to a carcinoma. Treatment is surgical.

B Clinical symptoms and signs of hormonal fluctuation

1. **Menstrual cycle changes.** An alteration in the character of established menstrual cycles is the **most common manifestation of perimenopause** occurring in up to 90% of women. These can include changes in cycle frequency, duration, and amount of blood flow which can be classified as normal or abnormal.
 - a. **Menorrhagia** is defined as increased blood flow (**more than 80 mL**) during regular ovulatory menses, or bleeding that lasts longer than 7 days and is considered abnormal. It may lead to anemia.
 - b. **Metrorrhagia** is bleeding at **irregular intervals or between menses**. Shortening of cycle length is a common change reported early in the menopausal transition. Cycle length remains longer than 21 days but is typically shorter than cycles experienced during the reproductive years. Cycles are ovulatory with a shortened follicular phase.
 - c. **Oligomenorrhea is the decreased frequency of menstruation and is more common in the late perimenopause.**
 - d. **Amenorrhea** is the absence of menses.
2. **Other symptoms.** Many women who are still menstruating experience a variety of symptoms traditionally attributed to menopause.
 - a. **Hot flashes** are symptoms of vasomotor instability. This is the second most common perimenopausal symptom, reported by 75% of perimenopausal women. Hot flashes can come and go over time and are not consistent from cycle to cycle. They typically are present for up to 2 years after the FMP, but may persist for up to 10 years. When they occur with sleep and are associated with perspiration, they are called **night sweats**. Peripheral vasodilation is associated with a rise in skin temperature, resulting in a hot flash. There may also be a modest increase in heart rate at the same time.
 - b. **Headaches** may worsen during perimenopause, and then improve again after menopause. There may be a hormonal link, but this has not been well studied.
 - c. **Sleep disturbance.** Interrupted sleep, with or without hot flashes, is reported by one-third to one-half of U.S. women in this age group.

- d. **Mood disturbance** is reported by 10% of perimenopausal women. This includes symptoms of irritability, depression, insomnia, fatigue, and difficulty with memory or concentrating. Sleep deprivation and midlife stresses may be strong contributing factors. There is no evidence that cognitive function actually deteriorates with perimenopause or menopause but some studies have shown changes in memory.
- e. **Sexual function** such as libido, arousal, and vaginal lubrication and elasticity can be affected by the onset of perimenopause. These changes can be due to many causes, including hormonal fluctuation, medications, sleep disturbance, loss of partner, and life stresses.

C Treatment

1. **Progestogen (natural progesterone or synthetic progestin) supplementation.** Periodic administration of a progestogen is used to treat conditions associated with estrogen excess.
 - a. **DUB** can be treated with cyclic progestogen for 12- to 14-days each month leading to the orderly sloughing of the endometrium. Therapy may also be administered continuously, preventing withdrawal bleeding. These therapies decrease the incidence of anovulatory uterine bleeding and the development of endometrial neoplasia.
 - (1) **Medroxyprogesterone acetate (MPA)** is the most commonly used progestogen for DUB. Therapy may be used for only one cycle, continued cyclically until there is absence of withdrawal bleeding, or used continuously to suppress bleeding altogether. Absence of withdrawal bleeding signifies a reduction of estrogen levels to the menopausal range.
 - (2) **Norethindrone acetate**, also a progestin, can be used as an alternative to MPA.
 - (3) **Oral micronized progesterone**, derived from plant sources, is also an alternative.
 - (4) **The progestin-containing intrauterine system** delivers continuous low-dose progestin (levonorgestrel) directly to the endometrium. Ninety percent of women who use it have a reduction in blood flow and 20% have complete absence of any bleeding.
 - b. **Simple and complex hyperplasia** may be treated effectively with progestogen supplementation. Treatment with progestin or progesterone as described for DUB is prescribed. Follow-up biopsy is performed after 3 months of treatment to verify resolution of the hyperplasia.
 - c. **Complex hyperplasia with atypia** may be treated with high-dose progestogen if surgical therapy is not an option, once the presence of carcinoma has been excluded by such methods as ultrasonography, hysteroscopy, and D&C. Follow-up biopsy after 3 months of treatment is mandatory to verify resolution.
2. **Combination (estrogen–progestin) hormonal contraceptives** are useful for both contraception and treating symptoms in perimenopausal women who are normotensive nonsmokers without other risk factors. Choices include oral contraceptive pills, vaginal ring, and contraceptive patch.
 - a. Low-dose combination hormonal contraceptives (less than or equal to 35 µg ethinyl estradiol) can be an effective treatment for abnormal bleeding and hot flashes associated with perimenopause.
 - b. These medications are obviously also an effective method of contraception for women in whom this is still a concern. There is no increased risk using combination hormonal contraceptives in perimenopausal-aged women **without risk factors** compared to younger women.
 - c. Because **combination hormonal contraceptives** contain **five to seven times the estrogen equivalent of postmenopausal hormone therapy**, it is desirable to change therapy with the onset of menopause. FSH is not a reliable test for evaluating or predicting menopause status and the need for contraception. One suggested option is to continue combination hormonal contraception in women who tolerate it and have no risk factors until the average age of menopause.
3. **Hormone therapy (HT)** refers to the combined use of estrogen and progestogen in subcontraceptive doses. **Estrogen therapy (ET)** refers to the use of estrogen without a progestogen, usually only given in women who have undergone hysterectomy.
 - a. **HT and ET** may be used to treat perimenopausal symptoms in women with oligomenorrhea before permanent cessation of menses. There are many variations in dose, drug types, and delivery systems for HT and ET.

- b. Progesterone is added to estrogen in women who have their uterus. **Unopposed estrogen** increases the risk of **endometrial neoplasia** in these women. The risk is related to duration of use and dose. The absolute risk of endometrial cancer is 1 per 1,000 in postmenopausal women. In general, the risk increases to 1 per 100 in women on unopposed estrogen.
- 4. Scheduled **nonsteroidal anti-inflammatory drugs (NSAIDs)** effectively reduce menstrual blood flow in 40% to 60% in women with ovulatory cycles. NSAIDs block prostaglandin synthetase activity and should be initiated at the onset of menses and given on a regular schedule until past the risk of heavy flow. NSAIDs may be useful in the treatment of menstrual migraines.
- 5. **Alternative therapies** such as herbal remedies, acupuncture, and non-Food and Drug Administration (FDA)-approved hormones require further study.

V

CLINICAL MANIFESTATIONS OF MENOPAUSE

- A Menopause is characterized by amenorrhea** Women may also experience hot flashes, night sweats, mood disturbances, headaches, and sexual dysfunction.
- B Target organ response to decreased estrogen** Estrogen-responsive tissues are present throughout the body. Chronic reduction of estrogen may result in any of the following manifestations:
 - 1. **Urogenital atrophy.** The vagina, urethra, bladder, and pelvic floor are estrogen-responsive tissues. Decreased estrogen levels after menopause result in a generalized atrophy of these structures. About 25% of women seek medical help for associated symptoms. These symptoms often improve with the use of topical or systemic estrogen.
 - a. There is a reduction in the thickness of **vaginal epithelium** and vaginal vascular flow and increased vaginal pH. The vaginal epithelium shows a loss of rugation and elasticity. After menopause, there is a shift in the maturation index, with a preponderance of immature cell types (basal and parabasal) over mature cell types (intermediate and superficial).
 - b. The vaginal walls lose elasticity and compliance; the **vagina becomes smaller**. This results in increased likelihood of trauma, infection, **dyspareunia** (painful intercourse), and painful pelvic examination.
 - c. The **labia minora** have a pale, dry, thin appearance, and there is a reduction of the fat content of the **labia majora**.
 - d. The **pelvic tissues and ligaments** that support the uterus and the vagina may **lose their tone**, predisposing to disorders of pelvic relaxation.
 - e. The **epithelium of the urethra and bladder** mucosa becomes atrophic; there is a loss of urethral and bladder wall elasticity and compliance.
 - f. **Urinary tract symptoms** resulting from changes in the mucosal lining of the urethra and bladder may lead to increased symptoms of dysuria, nocturia, urinary frequency, urgency, and urge incontinence.
 - g. Urinary conditions such as **urinary stress incontinence** may progressively worsen after menopause because of urethral changes and a loss of pelvic support to the bladder. There is an increased incidence of **asymptomatic bacteriuria** and urinary tract infection in the postmenopausal woman.
 - 2. **Uterine changes**
 - a. The **endometrial tissue becomes thin**, with atrophic histologic changes. With transvaginal ultrasound it should measure less than 4 mm.
 - b. The **myometrium atrophies**, and the **uterine corpus decreases in size**. There is a reversal of the corpus:cervical length ratio compared with the reproductive years.
 - c. The **squamocolumnar junction** of the cervix migrates higher in the endocervical canal; the cervical os frequently becomes stenotic.
 - d. **Fibroids**, if present, may reduce in size but do not completely disappear.
 - 3. **Breast changes**
 - a. Progressive fatty replacement of breast tissue with atrophy of active glandular units occurs, with regression of fibrocystic changes.

- b. After menopause, the mammographic appearance of the breast becomes progressively more radiolucent in response to decreasing sex hormone levels.
 - c. HT increases breast density and reduces the sensitivity of mammograms.
4. **Skin changes**
- a. Skin collagen content and skin thickness decrease proportionately with time after menopause.
 - b. Exposure to sunlight and cigarette smoke accelerate skin aging.
5. **Hair changes.** As estrogen decreases, circulating free androgens increase and the chance of developing increased facial hair and androgenic alopecia increases.
6. **Central nervous system (CNS) changes**
- a. Estrogen receptors are located throughout the brain. Cognitive function and memory may decline with advancing age as estrogen levels decrease.
7. **Cardiovascular disease (CVD)**
- a. The incidence of CVD increases after the age of 50 years in women, coincident with the age of menopause.
 - b. CVD is increased in women who have premenopausal oophorectomy.
 - c. CVD is the cause of the largest number of deaths of menopausal women. The mortality rate from CVD among American women is greater than the next 14 causes of death combined.
 - d. Endogenous estrogen appears to protect against CVD in premenopausal women. The increase in CVD seen after menopause has been attributed primarily to lack of estrogen. Estrogen has been believed to be protective for CVD in postmenopausal women. However, when estrogen is given to women in menopause it may increase the risk of cardiovascular events in women with established CVD rather than have a protective effect. This was suggested by the Womens Health Initiative (WHI) study which showed an increase in CVD from HT, particularly when started in women in the later postmenopausal period (i.e., after years of hypoestrogenism). However, subsequent evaluation of the data as well as other studies suggest that when estrogen is initiated in women in the early stages of menopause, before a substantial time of hypoestrogenism, there may be a protective effect.
8. **Vasomotor symptoms (VMSs) or hot flashes**
- a. **Hot flashes** are the second most common perimenopausal/menopausal symptom after abnormal bleeding. There are differences in incidence depending on the ethnic background of the woman. African American women report hot flashes the most frequently, followed by Hispanic, Caucasian, Chinese, and Japanese Americans. Differences in body mass index (BMI) may be a more important predictor of hot flashes than ethnic background.
 - (1) These symptoms have a circadian rhythm and are more frequent in the early evening. No clinical trials have confirmed that hot flashes are precipitated by caffeine, alcohol, or stress. They do appear to be exacerbated by cigarette smoking, sedentary lifestyle, and induced menopause.
 - (2) Hot flashes last for **1 to 2 years** in most women but may last for as long as 10 years.
 - b. Symptoms are the result of **inappropriate stimulation of the body's heat-releasing mechanisms** by the thermoregulatory centers in the hypothalamus. Although the core body temperature is normal, the body is stimulated to lose heat. The role of estrogen in causing VMSs is unclear, although it is known that estrogen receptors are found in this part of the brain. Estrogen administration diminishes the frequency and severity of symptoms in a dose-dependent manner.
 - c. VMSs are characterized by **progressive vasodilation of the skin over the head, neck, and chest**, causing a skin temperature rise. They are accompanied by reddening of the skin, a feeling of intense body heat, and perspiration. Palpitations or tachycardia may accompany the flush. The flush may last 1 to 5 minutes and recur with variable frequency. Flashes may vary from being annoying to totally disruptive to normal life function.
 - d. **Treatment**
 - (1) **Lifestyle changes**, such as regular exercise, avoiding smoking, wearing cool clothes, and lowering room air temperature, may help to minimize symptoms.

- (2) **HT and ET** consistently reduce or eliminate hot flashes, as do combined hormonal contraceptives such as birth control pill. Results are dose related, and optimal results may take several weeks.
 - (3) **Progestogens** are used to treat hot flashes in women in whom estrogen is contraindicated. Relief may not be as complete as that seen with ET.
 - (4) **Venlafaxine and selective serotonin reuptake inhibitors (SSRIs)**, given in low doses, have been effective in reducing or eliminating vasomotor instability in up to 60% of symptomatic women.
9. **Altered menstrual function.** If irregular vaginal bleeding or bleeding after 6 months of amenorrhea occurs, endometrial disease (e.g., polyps, hyperplasia, or neoplasia) must be ruled out.
10. **Sexual dysfunction** is a common complaint in the postmenopausal woman.
- a. Loss of libido is a significant concern in many women. It is felt due to lack of testosterone *and* estrogen production from the ovary. It is one of the most difficult conditions to treat.
 - b. **Dyspareunia** occurs due to atrophic changes in the vagina associated with hypoestrogenism. As a result there is decreased lubrication which leads to subsequent irritation and pain with sexual activity. Often vaginal lubricants are helpful, as is vaginal estrogen.
11. **Osteoporosis** is a disorder characterized by **compromised bone strength** predisposing to an **increased risk of fracture**. Bone strength reflects the integration of two main features: bone density and bone quality. Osteoporosis may be a primary disease state, resulting from estrogen deficiency or aging, or may be secondary to other diseases, conditions, or medications that affect calcium and bone metabolism.
- a. **Epidemiology and etiology**
 - (1) **Osteoporosis results when bone resorption outweighs bone formation.** Trabecular bone is at greater risk than cortical bone because it is more metabolically active and structurally more porous. Peak trabecular bone mass is reached in the late 20s and peak cortical bone mass in the early 30s. Thereafter, there is a gradual loss of bone with aging. **Bone loss is accelerated for the first 5 to 10 years after menopause** as a direct result of declining estrogen levels. Osteoporosis is more common in women than in men because of lower peak bone mass and higher rates of bone loss. Trabecular bone loss is more rapid in early postmenopause, resulting in an increase in distal forearm fractures after the age of 45 years and vertebral fractures beginning at the age of 55 years. Cortical bone loss is more gradual, resulting in an increased incidence of hip fractures in women after the age of 65 years.
 - (2) **Major risk factors for fracture** are advanced age, white or Asian race, and female gender as well as a personal history of fracture after the age of 50 years or a family history of osteoporosis or related fractures in a first-degree relative. Other risk factors include, but are not limited to current low bone mass, low BMI, inadequate calcium and vitamin D intake, sedentary lifestyle, cigarette smoking, hypothalamic amenorrhea, premature menopause, use of certain medications such as glucocorticoids or gonadotropin-releasing hormone agonists, medical conditions such as hyperthyroidism and hyperparathyroidism, and excessive use of alcohol.
 - (3) Osteoporosis has reached epidemic proportions in the United States, causing an estimated 1.5 million fractures annually. Four out of five Americans with osteoporosis are women. In 2002, an estimated \$18 billion was spent in direct care expenditures for osteoporotic fractures.
 - (a) Approximately 25% of white American women older than 60 years of age who are not treated have **vertebral compression fractures**. These are the most common fractures. There are about 700,000 osteoporosis-related vertebral fractures a year.
 - (b) Approximately 32% of untreated white American women older than 75 years of age suffer **hip fractures**; 24% older than 50 years of age will die in the first year after fracture. Of those who survive, 20% no longer live independently. There are over 300,000 hip fractures a year. Fractures also can occur at the distal forearm and other sites.
 - b. **Diagnosis.** Osteoporosis is a silent disease, becoming symptomatic only when a fracture occurs. Most common fractures are vertebral compression fractures (which can be symptomatic or

asymptomatic), a Colle's fracture of the forearm, or a hip fracture, although all bones are at risk.

- c. **Imaging modalities** can be used to detect bone loss and bones at risk for fracture at an earlier stage. However, not all osteoporotic fractures are associated with measured low bone mass.
 - (1) **Peripheral densitometry devices** such as quantitative ultrasound (QUS) can be used on the wrist, finger, or heel. Precision is poorer than with X-ray-based studies. QUS should not be used for monitoring therapy.
 - (2) **Dual-energy X-ray absorptiometry (DEXA)** is the most popular technique used today to measure bone mass. It is the "gold standard" to which all other methods are compared, having excellent precision and low radiation dose. Independent measurements can be made at the hip, spine, and, if indicated, distal forearm.
 - (3) **Quantitative computed tomography (QCT)** gives the most precise measurement of bone mass at specific sites. However, its use has been limited by expense and higher radiation dose.
- d. **The diagnosis of osteoporosis is based on DEXA T scores.** A T score is based on the mean peak bone mass of a normal young adult population and is expressed in standard deviations from the mean in this reference group. A T score = 0 is average, T score greater than 0 is above average, and T score less than 0 is below average. The lower the T score, the higher the risk of having a fracture is. **Osteopenia** (decreased bone density) is defined as a T score between -1 and -2.5. **Osteoporosis** is defined as a T score less than -2.5.
- e. **Prevention and treatment of osteoporosis** is important. The higher a woman's bone mass at the onset of menopause, the more bone she will have to lose to be at risk for osteoporotic fractures. Although no one can alter genetic predisposition, many lifestyle factors can affect fracture risk.
 - (1) **Adequate calcium intake** can be obtained through diet or supplementation; 1,500 mg of elemental calcium daily is recommended after the age of 50. This can be obtained through diet or supplements.
 - (2) **Vitamin D** is essential for the absorption of calcium and reduces fracture risk as well as the risk of falling; 1,000 IU/d is recommended, although up to 2,000 IU/d is safe. Vitamin D can be obtained through diet, supplementation, and sun exposure to the unprotected skin.
 - (3) Weight-bearing **exercise** has a positive effect on the skeleton and may reduce fracture risk and decrease the risk of falling.
 - (4) **Reducing the risk of falling** is essential for the prevention of fractures. This includes safety factors such as optimizing medications that may affect balance, removing dangerous obstacles, providing aids for ambulation and lighting, and using hip protectors.
 - (5) **Cigarette smoking and excessive alcohol consumption** increase the risk of fractures and are associated with lower bone mass.
- f. There are many medications used to prevent bone loss and/or treat low bone density. With the exception of teriparatide, these work by slowing bone breakdown during bone remodeling. They are called antireabsorptive agents.
 - (1) **Bisphosphonates** are very effective at preventing bone loss and decreasing the risk of fractures in people with low bone mass. Some are also approved for treating glucocorticoid-induced osteoporosis. Dosing is variable, ranging from once a week to once a year, depending on the type of bisphosphonate. They can be administered orally or intravenously.
 - (2) **Selective estrogen receptor modulators (SERMs)** such as raloxifene are taken orally daily and are related to tamoxifen. Raloxifene is approved for prevention of osteoporosis and is effective in reducing the vertebral fracture rate.
 - (3) **Calcitonin** nasal spray in limited studies has been shown to increase vertebral bone mass and decrease vertebral fracture risk.
 - (4) **HT and ET** are effective in preventing osteoporosis and reducing hip and vertebral fractures. However, due to other medication-associated risk factors, it is not recommended that they be used primarily for this indication unless other medications are not appropriate.

- (5) **Teriparatide (rhPTH 1 to 34)** is given as a daily injection for up to 18 to 24 months. It has an anabolic bone effect and decreases vertebral and nonvertebral fractures. Effect on hip is not proven.

VI

HORMONE THERAPY

- A Benefits and indications** The goals of HT are to (1) reduce symptoms resulting from estrogen depletion such as hot flushes, sleeplessness, and mood disorders; (2) treat vaginal dryness and atrophy; and (3) minimize the risk of disorders that may be more frequent during HT. Randomized controlled trials and observational studies published since 1998 highlighted the benefits of HT. However, studies published after 2002 suggested a small but significant increase in the rate of cardiovascular disease (CVD), stroke, venous thrombotic embolism, and breast cancer associated with use of HT. As a result of this information, the percentage of women aged 50 to 74 taking HT increased between 1995 and 2001 from 33% to 42%. By the mid-2003, however, the number had decreased to 28%. Hormone or estrogen replacement therapy is the most effective treatment for the relief of menopause-related symptoms and menopausal osteoporosis. However, each woman has a unique risk profile that may lead to more or less overall benefit from HT. It is important to consider the relative risks and benefits of HT for each patient before recommending these medications. If the decision is made to use HT, it should be given in the lowest doses for the duration of time needed to achieve the desired effect.
- B Recent studies** Table 37–1 lists recent large studies published on the use of HT in menopause. Data from these studies show that HT:
1. Is the most effective treatment for hot flushes.
 2. Significantly improves vaginal atrophy and dyspareunia.
 3. Has been shown to prevent and treat osteopenia and osteoporosis and decrease incidence of bone fractures.
 4. Improves cognition in women when started in the perimenopausal phase.
 5. Does not protect against CVD in menopause, though lipid profiles are improved. The WHI study's initial data evaluation showed a slight increase in nonfatal CVD events primarily in the first year of therapy. Death due to cardiac disease was not increased with HT in that study. However, review of the final data did not support the initial conclusion, that is, there was no increase in nonfatal CVD in women taking HT. It must be remembered that the average age of women in this study was 63 years, leading to one of the studies major criticisms.
 6. Increases the risk of stroke in users. The absolute risk is approximately from 20 to 25 cases per year among 10,000 otherwise healthy postmenopausal women.
 7. Increases the risk of venous thromboembolism (VTE). The incidence of VTE in healthy postmenopausal women is 16 to 22 cases per 10,000 women per year. HT increases this risk by twofold.

TABLE 37–1 Recent Large Studies Published on the Use of Hormone Therapy in Menopause

Study Title	Acronym	Year
Randomized Controlled Trials		
Postmenopausal Estrogen/Progestin Interventions trial	PEPI	1998
Heart and Estrogen/Progestin Replacement Study	HERS	1998
Women's Health Initiative Hormone Trials	WHI-HT	2002, 2004
Observational Studies		
The Nurses Health Study	NHS	2000
The Million Women Study	MWS	2003
Women's Health Initiative Observational Study	WHI-OS	2005

8. Estrogen alone is associated with an increased risk of developing endometrial cancer and should therefore not be used in women with a uterus.
9. Increases the incidence of breast cancer in users, but the risk returns to normal within 5 years after discontinuation. The effect of hormones on breast cancer risk is similar to that of alcohol consumption, obesity, and parity. The risk is slightly higher in those women using both estrogen and progestogen compared to estrogen alone. The risk of breast cancer in healthy postmenopausal women is approximately 30 cases per 10,000 women per year. The use of HT adds approximately 8 to 17 cases per 10,000 women per year to this baseline risk.

C Ongoing studies

1. **Kronos Early Estrogen Prevention Study (KEEPS)** is an ongoing study evaluating estrogen given either orally or transdermally to recently postmenopausal women to see if starting HT earlier modifies the effect on atherosclerotic disease. Progesterone is given to women who have their uterus.
2. The **Early versus Late Intervention Trial with Estradiol (ELITE)** study is currently evaluating women less than 6 years postmenopausal versus women greater than 10 years postmenopausal and the effect of estradiol on the development of atherosclerotic changes. Progesterone is given to women with their uterus.

D Risks and contraindications

1. **Absolute contraindications** include:
 - a. Undiagnosed abnormal genital bleeding
 - b. Known or suspected breast cancer or estrogen-dependent neoplasia
 - c. Active or history of thrombosis
 - d. History of stroke or myocardial infarction in the previous year
 - e. Active liver dysfunction or disease
 - f. Known or suspected pregnancy
 - g. Known allergy to HT/ET
2. **Endometrial cancer.** ET increases the risk of endometrial hyperplasia and carcinoma when used without progestogen in a woman with her uterus.
 - a. **Addition of a progestogen** for at least 12 days per month reduces that risk of endometrial cancer to less than 1% to 2%. There is a decreased relative risk of endometrial cancer in women who are on combined estrogen and progestin replacement therapy compared to women who take no HT.
 - b. In some cases, HT may be considered in women who have been successfully treated for stage I endometrial carcinoma and are asymptomatic.
3. **Commonly used schedules of HT**
 - a. The mainstay of HT is estrogen, which is usually given in a daily or continuous fashion. **Progestogen** is added to **ET** to prevent endometrial hyperplasia and carcinoma in women who have their uterus.
 - (1) **Cyclic therapy.** Continuous ET is given, and progestogen is added for 12 to 14 days each month. This results in a predictable withdrawal bleed following monthly cessation of progestogen in 80% of women. The duration and flow may decrease with time and cease altogether. Oral micronized progesterone, MPA, or norethindrone acetate for 12 to 14 days a month can be used.
 - (2) **Continuous combined therapy.** Progestogen given continuously with daily estrogen does not induce cyclic bleeding but is associated with unpredictable irregular bleeding in up to 40% of women in the first 6 months of therapy. By 1 year this is reduced to 10% to 25% of users. Oral micronized progesterone, MPA, or norethindrone acetate is taken daily with estrogen.
 - b. **Abnormal bleeding** that occurs with HT must be evaluated with **endometrial sampling** and possibly ultrasound to rule out endometrial disease. Bleeding that continues after sampling and appropriate management should be evaluated with **hysteroscopy** or **sonohysterography**.

- c. **Side effects** of progestogens may be associated with their mineralocorticoid antagonist activity. Premenstrual tension syndrome-like symptoms such as fluid retention and swelling, mood disturbance and depression, mastalgia, and headache are reported. Adjustment in dose, schedule, and route of administration may help relieve symptoms. Concerns about the possible effect of **progestogen with estrogen and increased risk of breast cancer have been raised by results of the WHI study.**
- 4. **Route of administration of systemic hormones** affects first pass through the liver, metabolism, and resulting serum levels of hormones. HT and ET may be administered through the following routes with FDA-approved products.
 - a. **Transdermal patches** contain either estrogen alone or estrogen plus progestogen and are changed once or twice a week, depending on the product.
 - b. **Percutaneous gel or emulsion** dispenses estrogen in metered doses and is used daily.
 - c. The **vaginal ring** contains estrogen only and is changed every 3 months.
 - d. **Oral estrogen or oral estrogen plus progestogen** is the most common route of administration. When administering HT, a single pill containing both estrogen and progestin may be given or they may be given in separate pills, on a daily basis.
- 5. **Local applications**
 - a. **Topical estrogen** is used intravaginally to treat symptoms of **urogenital atrophy** and **dyspareunia**. Estrogen-containing creams, tablets, and synthetic rings are available for this use. Peak systemic absorption is in the first few days of initial use. Once the vaginal mucosa becomes cornified, there is minimal systemic absorption of estrogen.
 - b. A **progestin-containing intrauterine device** may provide endometrial protection and avoid the side effects of systemic progestogen.

VII

RECOMMENDATIONS FOR CARE OF THE MENOPAUSAL WOMAN

A Health risk assessment and physical examination

1. Identification of risk factors in medical, surgical, social, family, and lifestyle history
2. Assessment for problems including abnormal bleeding, sexual function issues, sleep disturbance, urinary dysfunction, and hot flashes
3. Annual determination of height, weight, and blood pressure
4. Annual physical examination, including breast and pelvic examination

B Age-risk-appropriate screenings Evidence-based testing is performed to detect early disease in low-risk, asymptomatic patients.

1. Lipid profile assessment every 5 years beginning at the age of 45 years.
2. Fasting blood sugar screening every 3 years beginning at the age of 45 years.
3. Thyroid-stimulating hormone testing every 5 years beginning at the age of 50 years.
4. Controversy exists regarding frequency of mammogram screening:
 - a. The United States Preventative Services Task Force recently issued new guidelines suggesting targeted screening based on risk factors for women aged 40 to 49, and universal screening every 2 years beginning at the age of 50 years.
 - b. The American College of Obstetricians and Gynecologists recommends universal screening mammography annually beginning at the age of 40 years.
5. Cervical cytology every 1 to 3 years depending on age, risk, high-risk human papilloma virus DNA testing, and previous Pap history.
6. Osteoporosis screening beginning at the age of 65 years, and earlier in women with risk factors for fractures or in women whose decision to begin treatment would be influenced by screening results.
7. Routine screening for colon cancer beginning in low-risk women at the age of 50 years. Options include yearly fecal occult blood testing and/or flexible sigmoidoscopy every 5 years, colonoscopy every 10 years, or double-contrast barium enema every 5 years.

C Promotion of a healthy lifestyle

1. Discuss smoking cessation and alcohol limitation as needed.
2. Make nutritional assessment and recommendations about weight control, dietary fat, cholesterol, calcium, vitamin D, and caloric intake.
3. Assess contraceptive needs and risk for sexually transmitted diseases.
4. Make exercise assessment and recommendations.
5. Identify physical, emotional, and substance abuse risk and history, as well as high-risk behaviors.
6. Screen for symptoms of depression.
7. Counsel about prevention of falls in appropriate women.
8. Encourage home and occupational safety, as well as seat belt and safe firearm use.
9. Provide individually appropriate patient education.
10. Assess vaccination update status.



Study Questions for Chapter 37

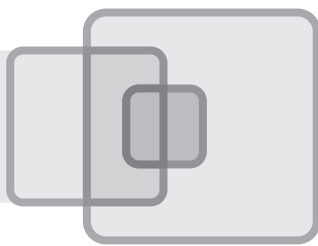
Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A 65-year-old obese, hypertensive woman with a history of premenopausal endometrial cancer at the age of 40 years treated by total abdominal hysterectomy and bilateral salpingo-oophorectomy presents with pain from a vertebral crush fracture. Which of the following is true?
 - A The patient should refrain from exercise to reduce the risk of another fracture
 - B HT is the preferred method of treatment to reduce the risk of future fracture
 - C Treatment of the endometrial cancer placed this patient at risk for osteoporosis
 - D Low-dose combination hormonal contraceptive is an acceptable treatment to treat osteoporosis in this patient
 - E The patient should stop using sunscreen to increase vitamin D exposure
2. A healthy 47-year-old G2P2 woman presents with a history of regular menses every 28 days since the age of 14 years until 6 months ago when her cycle frequency changed to every 22 days. Which of the following is true?
 - A The patient is at an increased risk of bone loss and fracture compared to women her age with menstrual cycles every 28 days
 - B Elevated serum LH as a result of decreased ovarian inhibin caused the change in her cycle frequency
 - C This is a typical perimenopausal woman
 - D The patient no longer needs contraception
 - E Anovulatory cycles are the likely cause of the change in her cycles
3. Cardiovascular disease is the number one killer of postmenopausal women. Which of the following is true?
 - A Estrogen has a protective effect against CVD in premenopausal women
 - B Total cholesterol levels are increased in women taking ERT
 - C HT does not affect established CVD
 - D The WHI study described an increase in deaths from CVD in women taking HT
 - E HT/ET is indicated for prevention of CVD
4. Inhibin plays a major role in the endocrine changes noted in the peri- and postmenopause. Which of the following statements are NOT true?
 - A The granulosa cells of the ovary secrete inhibin
 - B Inhibin has a negative feedback on FSH
 - C Inhibin levels begin to increase during the perimenopause
 - D Inhibin levels are not used in the diagnosis of menopause
 - E LH secretion is unaffected by the perimenopausal change in inhibin production
5. A 52-year-old woman who experienced menopause at the age of 50 years presents with a history of scant spotting 2 months ago. The spotting has not recurred. You should:
 - A Give her a progestin for presumed excess estrogen
 - B The presence of endometrial cancer needs to be assessed through a hysterectomy
 - C Reassure the patient that there is nothing to worry about since she did not experience heavy bleeding
 - D Ask the patient to call if the bleeding recurs
 - E Take a history, perform a physical examination, perform endometrial tissue sampling, and order a pelvic ultrasound or perform hysteroscopy



Answers and Explanations

1. **The answer is C** [V B 11]. The patient's treatment of her endometrial cancer would lead her to an iatrogenic menopause. As a result the patient was hypoestrogenic for a longer duration than most women who undergo spontaneous menopause. This hypoestrogenic state led to an acceleration of bone loss over a longer period of time. HT and combination hormonal contraceptives are contraindicated in an individual with a history of estrogen sensitive cancers. The patient does not need to stop exercising. Calcium and vitamin D in adequate amounts are necessary for all postmenopausal women but by increasing the risk of skin cancer. One should recommend vitamin D supplements if dietary intake is inadequate.
2. **The answer is C** [IV B 1]. This is your typical perimenopausal woman who is experiencing one of the first signs of this transition. Estrogen levels are normal or elevated so there is not an acceleration of bone loss. She is likely experiencing ovulatory cycles with a shortened follicular phase as a result of elevated FSH. The latter is increased because of reduced inhibin secretion by the ovary. The patient remains at risk for pregnancy and contraception should be employed if pregnancy is not desired.
3. **The answer is A** [V B 7]. Estrogen plays a protective effect in premenopausal women. Although there is no consensus regarding its effect in early postmenopausal women, it is known to increase cardiovascular events in postmenopausal women with established heart disease. Estrogen decreases total cholesterol and LDL and increases HDL. The WHI study did not report an increase in deaths from CVD in women taking HT.
4. **Answer is C** [II B 1]. Inhibin, which is secreted by the granulosa cells of the ovary and has a negative feedback on FSH, starts to decrease in the perimenopause. This leads to an elevation of FSH. Inhibin does not exert a negative feedback on LH. Inhibin levels are not used to diagnose menopause as they can fluctuate throughout a cycle and from cycle to cycle.
5. **The answer is A** [V B 9; IV A 2]. Any bleeding, including scant spotting, requires evaluation in a postmenopausal woman even if it only occurs one time. The presence of pelvic pathology needs to be investigated, including the possibility of endometrial cancer. This patient requires evaluation through endometrial sampling and uterine assessment. HT is contraindicated in individuals with unexplained vaginal bleeding. Hysterectomy is not the method used to rule out endometrial cancer.



Breast Disease

MARCIA BORAAS

I

INTRODUCTION

Most women who present with breast-related symptoms are primarily worried about the possibility of breast cancer, whether or not they specifically articulate this concern. A careful history and thorough physical examination are essential in discerning the etiology of any breast symptom, with breast imaging employed as appropriate. The responsibility of the health care provider includes not only symptom evaluation and treatment, but also effective communication of the findings and treatment plan to the patient, ensuring that the individual patient's specific questions and concerns are addressed. Documentation of these discussions is important.

A History

1. Pertinent aspects of the **patient's history** include age; age at menarche; parity, including age at first delivery; menopausal status; use and duration of hormonal medications; history of cysts or prior breast biopsy, including whether or not atypia was present; personal history of cancer, especially breast or ovarian.
2. **Family history** of cancer, particularly breast (unilateral or bilateral) and ovarian cancer, including age at diagnosis. Paternal family history is equally important to maternal, as breast cancer genetic mutations (BRCA1 and BRCA2) are autosomal dominant and can be passed down through either side of the family.
3. Detailed information regarding any **current breast problem** is also important, including information about onset, change over time, associated precipitating factors, and recent breast imaging results.

B Physical examination The intention of the breast examination is to thoroughly evaluate the glandular tissue—from the clavicle to the inframammary crease, the sternum to the latissimus muscle, and from the skin surface to the underlying chest wall. It is therefore important to examine the breasts, by inspection and systematic palpation, in the sitting as well as the supine position. Attention should be paid to the breast appearance, including the location of scars, skin changes (such as dimpling or retraction) and nipple changes (such as flattening of the nipple–areolar complex or excoriation). Size discrepancies between the breasts should also be noted, and whether they are recent or longstanding. Palpation should be directed not only to document discrete “lumps,” but also the underlying pattern of tissue density, as many women will have normal asymmetry in the glandular tissue distribution, that is, prominence in the upper outer quadrants, or superior to the inframammary crease. Lymph node-bearing areas in the axillary and supraclavicular regions should be carefully checked as well. Questionable findings require radiographic assessment and possible referral to a breast surgeon.

C Imaging Any breast-related symptom presents an opportunity to update routine breast cancer screening, with additional imaging tailored to the specific clinical situation.

1. Diagnostic mammogram is appropriate in women aged 30 years or above, combined with ultrasound (US) if a localized area of the breast is symptomatic.
2. Symptomatic women younger than 30 years are initially evaluated with US, as breast density in younger women makes mammography somewhat less sensitive, and the likelihood of cysts, which can be definitively diagnosed by US, is greater.

3. Because of the high false-positive rate, breast magnetic resonance imaging (MRI) should usually be obtained only after consultation with a breast surgeon.

II

CLINICAL ISSUES

A Breast abscess Breast infections which result in abscess formation typically arise in the postpartum setting, usually within several weeks of delivery, but sometimes during weaning. They are also seen, often as a recurring event, in the periareolar region of nonlactating women, or as isolated peripheral infections in postmenopausal or immunocompromised patients. Early initiation of appropriate antibiotics is essential, with aspiration or surgical drainage usually required once an abscess collection has formed.

1. Postpartum/lactational abscess
 - a. Tend to be centrally based—likely due to skin or nipple trauma from nursing
 - b. Typically due to skin organisms, usually *Staphylococcus aureus*
 - c. Methicillin-resistant *Staphylococcus aureus* is increasingly common, and should be included in antibiotic coverage
 - d. US can be helpful to assess the presence and extent of abscess formation
 - e. Needle aspiration should precede and may preclude the need for surgical drainage.
 - f. Continued nursing is usually possible, but mechanical pumping may be necessary on the affected side until the acute inflammation has subsided.
2. Recurrent periareolar abscess
 - a. This syndrome usually occurs in women during their reproductive years, often with premenstrual flare of symptoms, and is associated with alterations in subareolar ductal architecture such as duct ectasia.
 - b. Bacterial cultures yield variable organisms including anaerobes, or may be sterile.
 - c. Repeated infections may lead to cutaneous fistula formation and require treatment with surgical duct excision.
3. Peripheral breast abscess
 - a. Usually occurs in postmenopausal women with no clear underlying cause, although factors such as diabetes or steroid use may contribute
 - b. Skin bacteria, usually *Staphylococcus aureus*, are typically confirmed by culture

B Nodularity/breast masses

1. Breast tissue is a composite of glandular and adipose components and is normally lumpy with a “cobblestone” or “cottage cheese” texture. Most women will have a stable pattern of nodularity that may vary somewhat with menstrual cycling, hormonal medications, weight change, and other factors. More discrete masses or progressive focal areas of thickening require evaluation, although most palpable breast masses are benign. In general, they can be cystic (fluid filled) or solid.
 - a. Benign breast masses are more likely to be soft or cystic, have regular borders, and be freely mobile.
 - b. Malignant breast masses more often exhibit irregular, hard edges, but can present with fullness rather than a discrete mass.
2. The most common benign conditions are listed below.
 - a. **Fibrocystic change** (rather than fibrocystic “disease”) generally refers to prominent normal, sometimes asymmetric, glandular thickening—often most pronounced in the upper outer quadrants of the breasts—which can be firm (dense) in texture and sometimes associated with tenderness or true cyst formation. The incidence of these findings is greatest in premenopausal women, as breast gland tissue is hormonally sensitive and responsive to hormonal variations. Histologically, the tissue may demonstrate ductal or lobular hyperplasia, sclerosing adenosis, or unremarkable glandular elements.
 - (1) Although fibrocystic change was once thought to be a precursor of carcinoma, this belief has been dispelled in the literature. The only risk associated with pronounced fibrocystic change is the potential difficulty with clinical breast examination (CBE), as malignancy may be more difficult to detect in dense glandular tissue.

- (2) The most important aspect of evaluation is accurate diagnosis. Physical examination should be documented, and appropriate imaging studies performed. If questions still exist as to the nature of the findings, breast surgical consultation is advisable.
3. **Breast cysts** are dilated, fluid-filled duct spaces, most commonly seen in pre- and perimenopausal women. They may develop and resolve spontaneously in a short period of time, often in association with the menstrual cycle. On clinical examination, cysts generally feel smooth, round or oval in shape, with distinct borders, and may be soft or firm in texture.
 - a. Cysts have no known connection to breast malignancy, but can become inflamed and painful, especially premenstrually.
 - b. When a suspected breast cyst is palpated on clinical examination, cyst aspiration or focused US should be performed to confirm the diagnosis.
 - (1) Aspiration of a cyst is indicated if the diagnosis is in doubt or to relieve pain. Fluid that is bloody needs to be sent for cytology as risk of cancer increases. If cyst recurs, fluid also needs to be sent for cytology. If recurs again then excisional biopsy is necessary.
 - (2) Ultrasonic evaluation is useful to confirm that a palpable lesion is cystic or solid.
 - (3) Mammography should be considered any time a breast mass is found, and always if a cystic-appearing lesion yields no fluid on aspiration or is not cystic on US.
4. **Fibroadenomas** are solid, benign lesions, most common among women in their teens, 20s, and 30s. They may be single or multiple, and are well-circumscribed, smooth, freely movable, and sharply margined.
 - a. There is no known connection between fibroadenomas and breast cancer.
 - b. Biopsy is mandatory, even if the clinical findings are consistent with a fibroadenoma, as the clinical impression must be confirmed pathologically. Biopsy can be accomplished with fine-needle aspiration (FNA) cytology, core biopsy, or excisional biopsy, depending on the age of the patient, size of the lesion, and presence of symptoms.
5. **Fat necrosis.** This condition is the delayed result of direct tissue trauma (i.e., seatbelt injury in a motor vehicle accident, prior radiation, or surgery). It may present as an irregular, possibly tender, firm mass, with no progressive increase in size over time.
6. **Lipomas** can occur in any area of adipose tissue, including the breast. They have the typical clinical presentation of a soft, well-circumscribed mass, associated with a negative mammogram and usually a normal US.
7. **Mondor's disease** refers to thrombophlebitis of the thoracoepigastric vein. This condition can follow trauma (including surgery) or can be idiopathic. The physical examination shows linear skin indentation associated with a vertically oriented, often tender cord along the inferior breast, best seen with the patient's arm raised. The condition is benign and self-limited, although treatment with heat and analgesics is helpful.

C Nipple discharge Approximately 3% to 10% of breast complaints involve nipple discharge. Most nipple discharge is due to a benign cause, either extrinsic (hormonal, medications) or intrinsic (duct ectasia, papilloma). The history should include the color of the discharge, whether or not it is spontaneous or elicited, bilateral or unilateral, multiduct or single duct. Physical examination should ascertain whether there is a trigger point for the discharge, or an associated mass. Nipple discharge that is surgically significant is typically serous or bloody, unilateral, single duct origin, and spontaneous.

1. **Galactorrhea** (milky secretions in a woman who is not breastfeeding) is the most common presentation of extrinsic nipple discharge. It is usually bilateral, arises from multiple ducts, and results from increased levels of prolactin due to a pituitary adenoma, thyroid disease, or as a side effect of medications such as phenothiazines, tricyclic antidepressants, or oral contraceptives. A prolactin level and thyroid function tests should be obtained. Treatment is directed at the underlying cause.
2. **Intraductal papilloma** is the most common cause of a bloody or serous heme + nipple discharge, that is, usually single duct, spontaneous, and may be associated with a palpable mass. Surgical excision is mandatory to exclude the presence of papillary carcinoma or ductal carcinoma in situ (DCIS).

3. **DCIS** will occasionally present as a nipple discharge with characteristics similar to that of an intraductal papilloma.
4. **Paget's disease** is a condition affecting the skin of the nipple, causing erythema, scaling, and excoriation. It does not represent true nipple discharge, but may produce weeping from the surface of the nipple mimicking a discharge. It is usually associated with underlying breast malignancy.

D Breast pain Women commonly seek advice from physicians for breast pain (also known as mastalgia or mastodynia), which may be cyclic or noncyclic in nature. Breast pain most often occurs in women in the reproductive years (i.e., before menopause) and is usually associated with benign conditions or remains unexplained. Breast cancers can occasionally present with localized pain. The most important aspect in the management of breast pain is to rule out a serious underlying abnormality. Persistent unexplained pain should be evaluated by a breast surgeon, and will occasionally warrant MRI.

1. **Cyclic mastalgia.** Symptoms of breast pain often occur during the premenstrual or menstrual phases of the menstrual cycle. Pain is usually bilateral but often asymmetric, and occasionally unilateral. Although this cyclic pattern suggests a hormonal etiology, no laboratory tests have confirmed that hormonal variation plays a causal role. If there is no underlying pathology, then treatment is as follows:
 - a. Analgesics, especially nonsteroidal anti-inflammatory drugs (NSAIDs)
 - b. Vitamin E supplementation
 - c. Evening primrose oil
 - d. Instituting or changing a hormonal contraceptive medication
2. **Noncyclic mastalgia.** This breast pain is constant or episodic, and unrelated to menses. If the pain is focal, an underlying cause is often identified. Generalized noncyclic mastalgia is harder to treat, and may reflect increased breast sensitivity rather than specific pathology. Common causes include costochondritis, trauma, and breast cysts. Rarely esophageal spasm, GERD, and gallbladder disease will produce symptoms perceived as originating within the breasts. Treatment is directed at the underlying cause.
3. **Breast pain as the presenting symptom of underlying malignancy** is uncommon and has no "typical" character, but is likely to be unilateral, localized, and persistent. Breast surgery consultation and imaging, obtained routinely in the evaluation of persistent focal pain, should identify the underlying cancer.

III

BREAST CANCER

While evaluation and treatment of diagnosed breast cancer is typically the realm of breast specialists, breast cancer screening and evaluation of the initial clinical or radiographic abnormality is often the responsibility of the patient's primary physician or gynecologist. In this setting, a knowledgeable physician has the opportunity to support and advise the patient, setting the stage for successful care.

A Screening There is general agreement among professional organizations such as the American Cancer Society (ACS), American Congress of Obstetrics and Gynecology (ACOG), and the American Society of Breast Surgeons with regard to clinical and mammographic screening for breast cancer. Recent guidelines issued by the U.S. Preventive Services Task Force (USPSTF; November 2009) have suggested changes in screening practices but, due to concern about data accuracy and objections from reputable individuals and societies, no official change in screening recommendations has occurred (USPSTF recommendations are noted below for comparison, but are not to be followed).

1. **Breast self-examination (BSE)**
 - a. Women should know how their breasts normally look and feel and report any breast change promptly to their health care provider. BSE is an option for women starting in their 20s (ACS)
 - b. BSE has the potential to detect palpable breast cancer and can be recommended (ACOG)
 - c. BSE discouraged (USPSTF)

2. CBE by a health care provider
 - a. CBE about every 3 years for women in their 20s and 30s and every year for women aged 40 and older (ACS)
 - b. CBE every year for women aged 19 or older (ACOG)
 - c. CBE not recommended (USPSTF)
3. Mammography
 - a. Yearly mammograms are recommended starting at the age of 40 years and continuing for as long as a woman is in good health (ACS)
 - b. Screening mammography every 1 to 2 years for women aged 40 to 49 years. Screening mammography every year for women aged 50 years or older (ACOG)
 - c. Screening mammography every 2 years for women aged 50 or older. No mammograms for women aged 40 to 49 unless high risk (USPSTF)
4. High-risk screening
 - a. The ACS recommends that some women—because of their family history, a genetic tendency, or certain other factors—be screened with MRI in addition to mammograms. The number of women who fall into this category is small: less than 2% of all the women in the United States (ACS).
 - b. There is general consensus that women with BRCA1 and BRCA2 mutations receive annual breast MRI screening, alternating by 6 months with mammography, and that screening begin by age 30, or 5 years earlier than the youngest age of breast cancer diagnosis within the affected family.
5. Other imaging modalities (US, breast-specific gamma imaging, thermography) have no proven role in breast cancer screening.

B Genetic breast cancer risk Most breast cancer, including familial breast cancer, occurs without a measurable indicator of risk. In 5% to 10% of diagnosed women, breast cancer can be attributed to a detectable mutation in one of the known BReast CAncer genes, known as BRCA1 or BRCA2. These genes are located on chromosomes 17 and 13, respectively, and increase a woman's lifetime risk of breast cancer from 13% to 60% to 80%, as well as increasing the risk of other cancers, particularly ovarian and colon malignancies, and prostate and breast cancer in men. A deleterious mutation can be inherited from either parent and follows an autosomal dominant pattern, so that a single abnormal gene copy will confer the increased risk as noted in Table 38–1.

1. **Evaluation for genetic testing**, which is complex, expensive, and not always covered by insurance, should occur in the context of a formal risk evaluation program or after discussion with a trained genetic counselor. In general, **candidates for BRCA mutation testing are as follows**:
 - a. Family history of multiple family members with breast cancer, often with young (less than 50) age at diagnosis
 - b. Family history of bilateral or sequential breast cancers in a single individual
 - c. Family history of any ovarian cancer, or breast and ovarian cancer in a single individual
 - d. Family history of male breast cancer
 - e. Individuals diagnosed with breast cancer by the age of 40 years
 - f. Individuals of Ashkenazi Jewish ethnicity
2. Results of testing can yield true positive, true negative, or uncertain results.
Ideally, the initial testing should be performed on an individual with a confirmed cancer diagnosis.

TABLE 38–1 BRCA 1 and BRCA 2 Lifetime Cancer Risk

BRCA 1 Lifetime Cancer Risk	BRCA 2 Lifetime Cancer Risk
Breast 60–80%	Breast 60–80%
Ovarian 40–45%	Ovarian 10–20%
Colon 10–15%	
Cervical, uterine, pancreatic, male breast cancer slight increase risk	Melanoma, pancreatic, male breast and prostate slight increase risk

- a. If initial testing is negative, no other family members need to be tested, as a BRCA mutation has been ruled out as the cause of the familial cancer.
 - b. If an affected family member tests positive for a deleterious mutation (true positive), other family members may choose to be tested. In this case, a negative test indicates that the individual did not inherit the familial risk and is a true negative.
 - c. If no individual with a cancer diagnosis is available or agreeable to testing, a negative test result is of uncertain significance since it cannot be proven whether a BRCA mutation is the actual cause of the familial risk. There are likely other genes which play a similar role, but which have not yet been identified and for which no testing is available. There are also BRCA mutations of uncertain significance which are not at this time associated with known cancer risk.
3. Specific recommendations for cancer screening and/or risk reduction will usually follow identification of a BRCA mutation.
- a. Breast cancer screening, as noted above, is initiated at an earlier age and usually includes annual breast MRI in addition to mammography.
 - b. Reduction in the risk of breast cancer can be achieved medically with Tamoxifen or Raloxifene (40% to 50% reduction) or surgically with bilateral simple mastectomies (90% to 95% reduction), and may be a consideration for some women. Breast reconstruction options have improved considerably in recent years, making prophylactic mastectomy a more reasonable choice than in the past. However, any elective intervention in a healthy individual requires careful evaluation of benefits versus risks.
 - c. On the basis of ovarian cancer risk, annual ovarian US, and/or prophylactic oophorectomy after childbearing may also be recommended.

C Diagnosis While therapy for breast cancer invariably requires consideration of surgery, surgical biopsy for the diagnosis of breast cancer is the exception rather than the rule. Core needle biopsy (8 or 10 gauge) directed by physical findings or image guidance is currently considered the standard of care. A small metallic clip is usually placed at the time of biopsy to identify the site on future radiographs. It is important to remember, however, that any “sampling” technique cannot exclude malignancy, and complete excision of a suspicious lesion is required if the core biopsy findings are indeterminate or inconsistent with clinical and radiographic information.

1. Stereotactic biopsy
 - a. Core needle biopsy performed under mammographic guidance
 - b. Typically used for biopsy of mammographic calcifications and masses not identified by US
 - c. Performed by breast imaging specialists, as well as breast surgeons with appropriate training and access to equipment
2. US-guided core biopsy
 - a. Preferred for any lesion visualized by US, usually complex or solid masses
 - b. Technically, the simplest approach and most comfortable for the patient
 - c. Frequently performed as an office procedure by breast surgeons as well as radiologists
3. MRI-guided core biopsy
 - a. Primarily utilized for lesions seen only on MRI, after negative “second look ultrasound” directed to the site of MRI enhancement
 - b. Requires specialized training and equipment, and should be performed by an experienced radiologist
4. Fine-needle aspiration
 - a. Provides less complete histologic information than an intact tissue core.
 - b. This technique is normally reserved for cyst aspiration or situations where bleeding from a larger bore core biopsy is a significant concern.
 - c. Results should be carefully correlated and consistent with other clinical and radiographic information before any action is taken.
5. Surgical biopsy
 - a. Appropriate when the results from a core needle biopsy are inconclusive, or a core needle biopsy is not technically possible due to location of the target lesion, or breast size.

- b. Localization of nonpalpable radiographic findings for surgical excision can be performed using any of the imaging methods noted above. It is often possible to place a guide needle for “needle localization” and surgical excision of lesions which are not technically accessible for core needle biopsy.

D Pathology Primary breast cancer is essentially adenocarcinoma arising from either the lobular (milk producing) or the ductal (milk conduit) components of the breast gland structure. About 20% of breast cancers are lobular and 80% have ductal histology. With both types, there is an “in situ” precursor to the invasive version. With improved mammographic screening, the proportion of diagnosed in situ carcinoma has progressively increased, although invasive ductal carcinoma remains the most common breast cancer diagnosis. Pure in situ carcinoma is correctly considered a local problem, with an excellent long-term prognosis. Invasive carcinoma requires attention to both local and systemic recurrence risk.

1. Ductal carcinoma

- a. In situ ductal carcinoma (DCIS). Considered a direct precursor to invasive ductal carcinoma.
- b. Invasive ductal carcinoma (IDC). Most frequently diagnosed type of breast cancer, but demonstrates widely variable behavior.

2. Lobular carcinoma

- a. In situ lobular carcinoma (LCIS). Considered a “risk factor” for future breast cancer rather than a direct precursor. Lifetime breast cancer risk is 20% to 25%.
- b. Invasive lobular carcinoma (ILC). Compared to IDC, more often multifocal or regional distribution within the breast.

3. Additional classifications

- a. Colloid, medullary, papillary, and tubular cancers are versions of invasive ductal carcinoma with specific histologic characteristics and potentially more favorable behavior and prognosis. They are evaluated and treated as IDC.
- b. Inflammatory breast cancer is also a version of IDC which presents a clinical appearance similar to cellulitis, associated with tumor in dermal lymphatic channels. It demonstrates a particularly aggressive behavior, and has a poor prognosis.
- c. Phyllodes tumors have a clinical presentation similar to fibroadenomas, but differ histologically and may demonstrate rapid growth. They typically are benign or “low grade,” but may be malignant or “high grade,” accounting for approximately 1% of diagnosed breast cancers.

E Evaluation/imaging Testing following a new diagnosis of breast cancer is intended to determine the extent of disease, both local and systemic, in order to design the most appropriate individual treatment plan. While “early stage” (I–II) breast cancer does not require extensive testing, any suggestive symptoms or abnormal screening studies should be thoroughly evaluated to exclude a malignant etiology. The most common sites of distant breast cancer metastasis are the lungs, liver, and bones.

1. Local/regional evaluation:

- a. Bilateral mammography is essential to evaluate for multicentric or bilateral abnormalities with specific evaluation of any findings, including biopsy, as necessary.
- b. Use of diagnostic breast MRI in this context is not standard, but may be indicated in high-risk women, young women, women with mammographically dense breasts, or with lobular cancer.
- c. Additional modalities, such as PET mammography (PEM) or breast-specific gamma imaging (sestamibi), have no confirmed utility in evaluating a diagnosed breast malignancy.
- d. Axillary node evaluation is indicated in the presence of invasive carcinoma to exclude regional lymphatic spread. While US-guided FNA of a clinically suspicious node is useful and considered definitive if cytology is positive, staging is usually accomplished with sentinel lymph node mapping/biopsy which will be discussed under surgical therapy.

2. Systemic evaluation:

- a. Chest X-ray, CBC, LFTs are routine after any invasive breast cancer diagnosis to screen for lung, bone marrow, and liver metastases.

- b. Bone scan is appropriate in the presence of more aggressive tumors or if symptoms are present.
- c. CT, MRI, PET scans are not routinely obtained without specific indications, but may be necessary to completely evaluate symptoms or abnormal findings on screening studies.

F **Treatment of** in situ carcinoma is generally limited to local therapy (DCIS), or risk reduction interventions (LCIS), while early stage (I–II) invasive carcinoma generally requires a combination of local and systemic therapy for optimal success. More advanced local disease (Stage III) is typically approached with systemic therapy as the initial intervention followed by curative surgery and radiation based on treatment response. Breast cancer which is metastatic at presentation is not treated for cure, but interventions are directed at controlling disease progression and preventing specific complications (i.e., pathologic fractures). This following information is primarily focused on the local therapy of early stage invasive breast carcinoma.

1. Local therapy consists of surgery, with or without radiation therapy, and is intended to eradicate the primary tumor and minimize the risk of local/regional recurrence. Historically, this has encompassed the primary tumor site and the unaffected breast tissue which remains “at risk.” The two primary options for local therapy are “lumpectomy,” that is, breast conservation and mastectomy.
 - a. **Breast conservation (lumpectomy)** requires surgical excision of the primary tumor with clear microscopic margins, generally followed by radiation therapy to eradicate potential residual microscopic disease in the breast. Axillary staging is typically combined with the breast surgery as a single procedure when invasive cancer is present.
 - (1) Breast surgery (lumpectomy, partial mastectomy, quadrantectomy) generally performed as an outpatient procedure, with the intention of preserving a relatively normal appearing breast.
 - (2) Sentinel lymph node biopsy (SNB) has essentially replaced axillary dissection for detection of regional lymphatic tumor spread. Its accuracy (98%) is predicated on the fact that nearly all lymphatic drainage from the breast parenchyma exits through a limited number of “sentinel” nodes, typically located in the low axilla. These are understood to be the nodes most likely to contain any migrating tumor cells, and accurately predict the status of the remaining nodes.
 - (3) Radiation, with rare exceptions, follows a successful lumpectomy and generally has been shown to decrease local recurrence from 30% to 40% to under 10%.
 - b. **Mastectomy** is surgical removal of both the tumor and the healthy, “at risk,” residual breast tissue. It generally eliminates the need for radiation, and coordination with a plastic surgeon to offer immediate reconstruction is appropriate in most circumstances. In the presence of invasive cancer, sentinel node mapping and biopsy should be performed either in advance or at the time of mastectomy.
 - (1) **Types of mastectomy**
 - (a) Simple mastectomy—removal of the breast only, including all detectable breast glandular tissue, but without lymph node dissection.
 - (b) Modified radical mastectomy—removal of the breast and adjacent axillary nodes.
 - (c) Radical mastectomy—removal of the breast, regional nodes, and pectoral muscle(s) with variable amounts of skin. Historically effective but now rarely indicated.
 - (d) Skin sparing mastectomy—appropriate in the context of immediate breast reconstruction, and refers only to the incision through which the appropriate mastectomy is performed.
 - (e) Nipple sparing mastectomy—breast removal is accomplished through a periareolar or inframammary surgical incision without any skin resection and with preservation of the nipple, combined with immediate reconstruction.
 - (2) **Reconstruction** of the breast after mastectomy may be immediate (performed as a combined procedure) or delayed. There are two main categories of reconstruction:
 - (a) Implant reconstruction—similar to breast augmentation with placement of a subpectoral silicone or saline implant, usually following a period of gradual filling of a temporary “expander” implant placed at the time of mastectomy.

- (b) Autologous tissue transfer—utilizes the patient’s own adipose tissue to recreate the breast mound, usually taken from the lower abdomen (TRAM flap), or from the gluteus or inner thigh. Earlier abdominal pedicle flaps are now being replaced by microvascular “free flaps,” including the muscle sparing TRAM, DIEP, and SIEA as the vascular anatomy allows.
 - (c) Postmastectomy radiation is indicated when the extent of disease suggests an increased risk of local recurrence.
- 2. **Systemic therapy** is intended to minimize the risk of recurrence at sites distant from the breast/chest wall, and consists of oral or intravenous medication which will reach sites of potential metastases through the blood stream. On the basis of tumor staging and characteristics, appropriate treatment may include hormonal therapy only, chemotherapy only, or a combination of both. All patients with invasive carcinoma should consult with a medical oncologist when adequate pathologic staging information is available, to complete treatment planning.
 - a. Hormonal therapy
 - (1) Appropriate consideration in all estrogen receptor(ER) or progesterone receptor (PR)+ invasive breast cancer, but ineffective in tumors which do not express measurable hormone receptors.
 - (2) Tamoxifen is standard for premenopausal women.
 - (3) Aromatase inhibitors offer equivalent or improved outcomes to Tamoxifen for postmenopausal women.
 - b. Chemotherapy
 - (1) Multiple regimens are available for women with ER/PR– tumors, or women with high risk ER/PR+ disease, most commonly utilizing Adriamycin, Cytosan, and taxanes; duration of treatment and side effects are specific to the medications used.

G Follow-up Following successful completion of initial therapy, most women are placed on a specific program of clinical examination and testing which is more frequent during the first 2 to 3 years when risk of recurrence is highest. Contrary to some malignancies, recurrent breast cancer risk continues past 5 years, but with progressively decreased incidence. The follow-up protocol may vary, but in general includes the following:

- 1. Local/regional evaluation
 - a. CBE every 3 to 6 months for 2 to 3 years, then every 6 to 12 months. Routine monitoring may be performed by the patient’s primary physician or gynecologist if there is no ongoing hormonal therapy.
 - b. Mammography is performed annually after a stable radiographic appearance of the treated breast is established.
 - c. Ongoing additional breast screening is determined by the patient’s original breast cancer risk.
- 2. Systemic evaluation
 - a. Testing as appropriate to monitor any long-term hormonal therapy (DEXA scan).
 - b. Evaluation of any new or progressing symptoms as indicated.
 - c. Routine use of tumor markers, CT or PET scanning, or other testing in an asymptomatic woman has no known benefit and is not recommended.



Study Questions for Chapter 38

Directions: Match the appropriate hormone(s), substance, or enzyme (which you could measure) with the description that is most likely to account for excessive hair growth in a woman. Each answer may be used once, more than once, or not at all.

1. A 28-year-old woman, gravida 2, para 2, presents to your office for a routine evaluation and you find an abnormality on her breast examination. She is asymptomatic, was unaware of the mass, and has no medical problems. There is no history of breast or ovarian cancer in her family. Her examination is notable for a 2-cm mass in her right breast that is smooth, mobile, and nontender. Your next step is:

- ☐ A Reassure her that the mass is benign
- ☐ B Recommend vitamin E
- ☐ C Obtain an US of the mass
- ☐ D Refer her to a breast surgeon for excision of the mass
- ☐ E Recommend a mammogram

2. A 60-year-old woman, gravida 3, para 2, SAb 1, presents to your clinic reporting brownish red-colored discharge from her left nipple. Her past medical history and medications, respectively, are as follows: diabetes—oral hypoglycemic; hypertension—angiotensin-converting enzyme inhibitor; major depression—fluoxetine. She is also taking conjugated estrogen with medroxyprogesterone acetate daily. She is allergic to penicillin. She says her mother was diagnosed with ovarian cancer at the age of 71 years. What is the next best step in management?

- ☐ A Mammogram
- ☐ B Ultrasound
- ☐ C Referral to breast surgeon
- ☐ D Cessation of hormone replacement therapy
- ☐ E Fine-needle aspiration (FNA)

3. A 44-year-old premenopausal woman presents for evaluation of an area of thickening in the upper outer aspect of her left breast. She has a family history of breast cancer in her maternal grandmother and her mother, who tested positive for a BRCA1 mutation. The patient has not been tested. She has been aware of the left breast changes for 2 months, with some associated discomfort but no fluctuation with her periods. A screening mammogram performed within the last 3 to 4 months was negative. On physical examination there is glandular asymmetry in the left breast, but no discrete mass or regional adenopathy. What is the most appropriate immediate recommendation?

- ☐ A Bilateral breast MRI
- ☐ B Follow-up clinical examination in 3 months
- ☐ C Reassurance, ibuprofen
- ☐ D Left breast US
- ☐ E Referral for genetic testing

4. A 58-year-old woman with no family history of breast cancer is seen in your office after noticing a mass in the 7 o'clock radiant of the right breast. She gives a history of trauma to the area 1 month previously, after which she noted a “quarter size” lumpy area with no associated skin discoloration. A mass is confirmed on your clinical examination with no other findings. Her mammogram shows dense breasts with no discrete abnormality, but a definite hypoechoic area is seen on US in the area of the mass. An US-guided core needle biopsy reveals unremarkable breast tissue. Your next recommendation is:

- ☐ A Reassurance, routine breast follow-up
- ☐ B Warm compresses, anti-inflammatory medication
- ☐ C Repeat mammography and US in 6 months
- ☐ D Bilateral breast MRI
- ☐ E Referral to a breast surgeon for surgical excision of the palpable mass

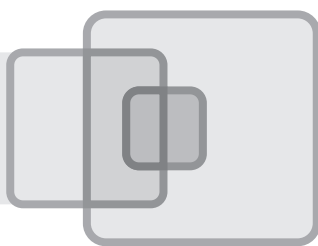
5. A very active, healthy 71-year-old woman, a long time patient in your practice, presents to discuss her recent breast cancer diagnosis. She was noted to have a 1.5-cm right periareolar mass which was confirmed on biopsy to be an invasive ductal carcinoma, ER-positive, PR-positive, HER-2 negative, with a low oncotype score. Her sentinel lymph node biopsy is negative and she expects to receive hormonal therapy rather than chemotherapy. She is uncertain about her choice of surgery. Which of the following options would **not** be appropriate for her consideration?

- ☐ A Lumpectomy with standard 6-week radiation therapy
- ☐ B Lumpectomy with accelerated partial breast irradiation
- ☐ C Mastectomy with chest wall radiation
- ☐ D Mastectomy alone without breast reconstruction
- ☐ E Mastectomy alone with immediate breast reconstruction



Answers and Explanations

1. **The answer is C** [II B 2, 3]. Although the mass has benign characteristics, it should be fully evaluated. An US of the mass would be the first step in evaluation. If the lesion is cystic then aspiration would be reasonable. If the lesion is solid then mammogram should be performed with appropriate diagnostic follow-up. Just reassuring the patient that the mass is benign is not appropriate. Vitamin E is an intervention for breast pain but not for a discrete mass.
2. **The answer is A** [II C]. The first step in management of any breast complaint is a clinical examination of the breast; however, a definitive diagnosis must be obtained, especially since the age of the patient and the bloody nature of the discharge places her at a higher risk of having a malignant breast lesion. The first step is obtaining a mammogram. An US could also be considered, especially if a mass is seen on mammogram. This patient should then be referred to a breast surgeon for further evaluation and probable biopsy. Cessation of hormone replacement therapy should be considered pending a definitive diagnosis.
3. **The answer is D** [III B, E]. This patient is at high risk for breast cancer based on her family history, and an aggressive approach to any breast change is indicated. Since a recent mammogram was negative, a directed breast US should be performed, with strong consideration of an MRI if the US is negative. In the long term, genetic testing should be offered, and annual screening MRI in addition to mammography may be appropriate based on risk. Reassurance and a 3-month follow-up would be reasonable if all imaging is negative and there is no clinical target for a biopsy.
4. **The answer is E** [III C]. There is discordance between the clinical and US findings which demonstrate a mass in the left breast, and the biopsy showing normal breast tissue. Since the core biopsy is a “sample” of the problem site, and since “normal breast tissue” does not explain the presence of a mass, surgical excision to allow histologic examination of the entire mass is necessary. If the core biopsy had shown findings consistent with recent trauma such as acute/chronic inflammation, local therapy and short-term follow-up to confirm resolution would be acceptable. There is no obvious role for MRI as it would not alter the need for surgical excision.
5. **The answer is C** [III F]. This woman has a very favorable breast cancer with an excellent prognosis, and could be well treated with any standard local therapy approach. In most cases, radiation is designed to treat residual breast tissue after a lumpectomy, and is not standard when the entire breast has been surgically removed. Radiation to the chest wall after mastectomy is reserved for patients with unfavorable tumor characteristics and a higher risk of local recurrence. It would not be appropriate in this setting.



Gestational Trophoblastic Disease

EVELYN B. MARSH • CHRISTINA S. CHU

I

INTRODUCTION

Gestational trophoblastic disease (GTD) is the general term for a spectrum of proliferative abnormalities originating from the trophoblast of the placenta.

A Classification (Table 39–1)

1. **Hydatidiform mole. Benign GTD** is also referred to as a hydatidiform mole, or more commonly a “**molar pregnancy**.” It is characterized by abnormal proliferation of the placental trophoblastic cells. These abnormal cells distend the uterus and secrete the polypeptide hormone **human chorionic gonadotropin (hCG)**, mimicking a normal pregnancy. Hydatidiform moles may be **complete (classic)** or **partial (incomplete)**.
2. **Gestational trophoblastic tumor (GTT)**. This malignant form of GTD, which arises from the trophoblastic elements of the developing blastocyst, retains the invasive tendencies of the normal placenta and remains able to secrete hCG. GTT can be either **metastatic** or **nonmetastatic**.

B Incidence

1. **Hydatidiform mole.** The incidence of benign GTD varies widely by region. It occurs in 1 of 1,500 pregnancies in the United States and in as many as 1 of 125 pregnancies in parts of eastern Asia.
 - a. **Complete moles** are the most commonly identified type of molar pregnancy. They are 5 to 10 times more common in pregnancies in women older than 40 years of age. Dietary factors, such as low intake of vitamin A and animal fat, are associated with this condition.
 - b. **Partial moles** are associated with oral contraceptive use and irregular menses.
2. **GTT.** Malignant GTD is identified in 1 of 20,000 pregnancies in the United States and can occur after any type of pregnancy.
 - a. Hydatidiform mole precedes GTT in 50% of cases.
 - b. Normal pregnancy precedes GTT in 25% of cases.
 - c. Abortion or ectopic pregnancy precedes GTT in 25% of cases.

II

HYDATIDIFORM MOLE (TABLE 39–2)

A Complete mole

1. **Origin.** In 90% of cases, an “**empty**” **ovum** containing no genomic DNA is fertilized by one **sperm**, which duplicates its DNA, leading to an abnormal 46,XX karyotype, with all DNA paternal in origin. In the remaining 10% of cases, the “empty” ovum is fertilized by two sperm, resulting in an abnormal 46,XX or 46,XY karyotype, again with all DNA of paternal origin. Thus, in a complete mole all the **chromosomes are paternally derived** (Fig. 39–1).
2. **Histologic features**
 - a. Marked edema and enlargement of the villi (hydropic villi)
 - b. Disappearance of the villous blood vessels

TABLE 39–1 Clinical Classification of Gestational Trophoblastic Disease**Hydatidiform Mole (molar pregnancy)**

Complete or classic
 Incomplete or partial

Gestational Trophoblastic Neoplasia

Nonmetastatic
 Metastatic
 Low risk (good prognosis)
 High risk (poor prognosis)

- c. Diffuse proliferation of the trophoblastic lining
- d. Absence of fetal tissue

3. Clinical features

- a. **Abnormal uterine bleeding** is the most common presenting symptom in the first trimester of pregnancy.
- b. **“Classic symptoms”** occurring later in pregnancy (often in the late first or second trimester) include heavy bleeding (90%), uterine size greater than expected for gestational age (40%), and lack of fetal heart tones. Additional classic symptoms that probably arise from stimulation by excessive hCG are hyperemesis gravidarum (nausea and vomiting; 25% in the past, but about 10% in the modern era), **theca lutein cysts** within the ovaries (50%), preeclampsia (rare in the modern era), and hyperthyroidism. Patients may present with passage of vesicular tissue from the vagina.
- c. A **diagnosis of complete molar pregnancy** is suspected when the **hCG level is greater than 100,000 mIU/mL** and when **ultrasound reveals a uterine cavity filled with small vesicles** rather than the expected gestational sac and fetus. Pathologic correlation and cytogenetic analysis for DNA content confirm the diagnosis.

4. Malignant potential

- a. Complete molar pregnancies result in malignant sequelae in 2% to 32% of cases.
- b. Up to 25% of cases may eventually display metastatic disease outside of the uterus.

B Partial or incomplete mole

- 1. **Origin.** A partial mole (see Table 39–2) is a normal ovum that is fertilized by two sperm. The resulting karyotype is 69,XXX, 69,XXY, or 69,XYY (Fig. 39–2).

TABLE 39–2 Comparison of Complete and Partial Mole

Feature	Complete Mole	Partial Mole
Age	Greater risk (5–103) >40 years	Not age related
Karyotype	90% XX, 10% XY All chromosomes paternally derived	XXX or XXY 1 chromosome set maternal; 2 chromosome sets paternal
Fetus	Absent	Present
hCG	Often >100,000 mIU/mL	Rarely elevated above normal levels for pregnancy
Primary symptom	Bleeding	Bleeding
Secondary symptoms	Large uterine size for gestational age Hyperemesis Theca lutein cysts Preeclampsia Hyperthyroidism	Rare
Risk of persistence (GTT)	20%	4%

hCG, human chorionic gonadotropin; GTT, gestational trophoblastic tumor.

Adapted from Lu KH, Goldstein DP, Bernstein MR, et al. Managing molar pregnancy. *O G B Manage* 1999;11:67–76.

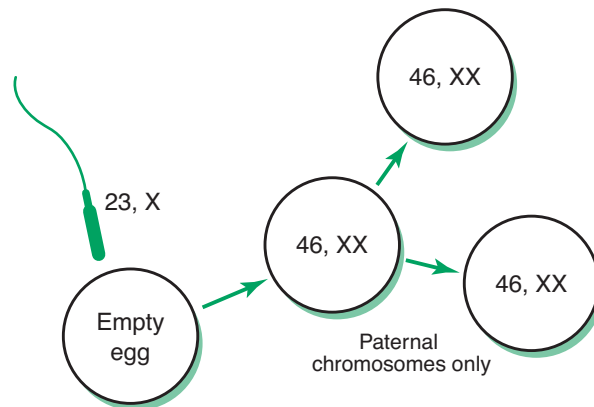


FIGURE 39–1 Chromosomal origin of a diploid complete hydatidiform mole. (Adapted from Kurman RJ. Blaustein's Pathology of the Female Genital Tract. 4th Ed. New York: Springer-Verlag, 1994:1051).

2. Histologic features

- Varying-sized villi, only some hydropic
- Focal trophoblastic proliferation
- Presence of an **umbilical cord, amniotic membrane, and fetus** that is usually not viable and has features of a triploid gestation

3. Clinical features

- Abnormal uterine bleeding** is the most common presenting symptom in the first trimester of a pregnancy, similar to complete moles.
- Excessive vaginal bleeding, hyperemesis, preeclampsia, hyperthyroidism, and ovarian cysts are rare.
- hCG is generally not significantly elevated**, and ultrasound may show a fetus as well as hydropic villi. Pathologic correlation and cytogenetic analysis for DNA content confirm the diagnosis.
- Many spontaneous abortions may represent undiagnosed partial moles.
- Case reports indicate that normal pregnancies coincident with partial moles have proceeded to term without adverse sequelae.

4. Malignant potential

- Less than 5% of partial moles progress to malignant disease.
- Only 1% of cases develop extrauterine metastases.

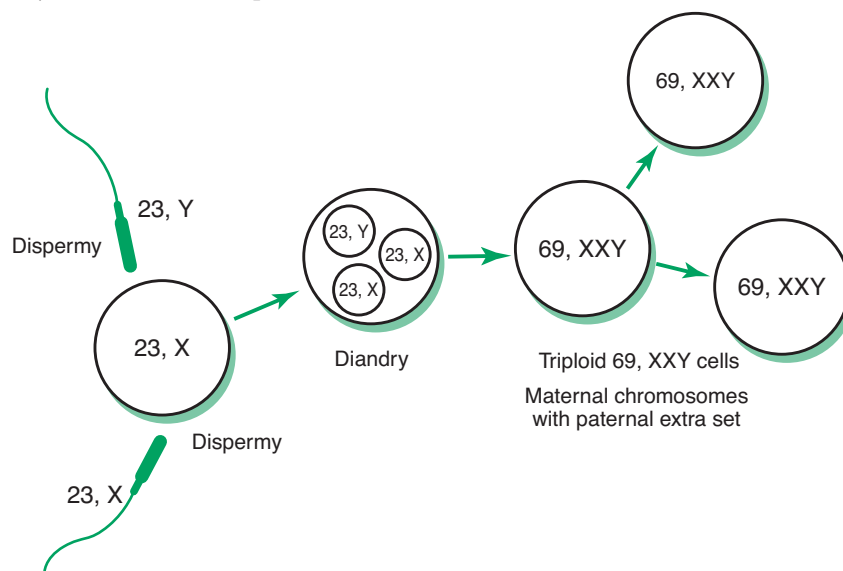


FIGURE 39–2 Chromosomal origin of a triploid partial hydatidiform mole. (Adapted from Kurman RJ. Blaustein's Pathology of the Female Genital Tract. 4th Ed. New York: Springer-Verlag, 1994:1052).

C Management of molar pregnancies (complete and partial)**1. Diagnostic studies**

- a. **Laboratory tests** include a complete blood count with platelets, quantitative hCG, coagulation studies, type and screen, baseline renal function and liver function studies, and thyroid function tests.
- b. **Imaging studies** include chest radiograph to evaluate for lung metastases and pelvic ultrasound.

2. Dilation and suction curettage of the uterus is the primary tool for evacuating a molar pregnancy even when the uterus has enlarged beyond the size expected for a pregnancy of 20 weeks. Simultaneous ultrasound monitoring during the procedure may be helpful.

- a. **Intravenous oxytocin** should be given to enhance uterine involution after the procedure to minimize blood loss.
- b. **Respiratory distress** resulting from fluid overload, emboli of trophoblastic tissue, and thyroid storm may occur in as many as 2% of patients in the perioperative period.
- c. Even large **theca lutein cysts** of the ovaries associated with molar gestation resolve as hCG levels drop. These cysts are not an indication for surgical intervention.

3. The risk of developing GTT after evacuation is 20% for a complete mole and 4% for a partial mole. **High-risk factors** associated with persistent disease include pretreatment hCG greater than 100,000 mIU/mL, theca lutein cysts greater than 6 cm, age older than 40 years, and previous molar pregnancy.**4. Hysterectomy** is a treatment option for patients who do not desire future fertility.**D Follow-up of a complete or partial molar pregnancy** After evacuation, the expected average time to complete elimination of hCG is 9 to 11 weeks. This period depends on the initial level of hCG, the amount of viable trophoblastic tissue remaining after evacuation, and the half-life of hCG. Follow-up of a molar pregnancy should include:

- 1. **Determinations of hCG** made at 48 hours postevacuation, then weekly until the results are negative for 3 consecutive weeks, then every month for 6 months, and then yearly. An increase or plateau in hCG indicates the development of **GTT** and necessitates the initiation of chemotherapy. Therefore, patients should be encouraged to avoid pregnancy until 6 to 12 months from diagnosis, so as not to confuse the diagnosis of possible GTT.
- 2. **Physical examination**, including a pelvic examination, at regular intervals until remission to ensure adequate involution of pelvic organs.
- 3. **Birth control** (recommended for 1 year). Oral contraceptives or medroxyprogesterone (Depo-Provera) injections are recommended. Pregnancy can be attempted after 6 to 12 months from the diagnosis, if there is no evidence of GTT requiring further treatment.
- 4. **Prophylactic chemotherapy is rarely recommended.** Most patients with molar pregnancies are cured with evacuation and do not require any therapy. Serial hCG determinations identify patients who develop GTT (20% of complete moles and 4% of partial moles). The toxicity from prophylactic chemotherapy can be severe, even leading to death.

E Future fertility

- 1. **Normal pregnancy** is the most likely result of future gestations.
- 2. **Risk of a second molar pregnancy** is 1%; in the case of two sequential molar pregnancies, the risk of a third molar pregnancy is 33%. Subsequent molar pregnancies may be complete or partial, regardless of the type of initial molar pregnancy.

III**GESTATIONAL TROPHOBLASTIC TUMOR**

- A Characteristics** Following a molar pregnancy, **GTT** (Table 39–3) may have the **histologic appearance of either a mole or choriocarcinoma**. After a normal pregnancy, abortion, or ectopic pregnancy, GTT always has the appearance of **choriocarcinoma**, or occasionally the aggressive **placental site trophoblastic tumor** variant of choriocarcinoma.

TABLE 39–3 Classification of Gestational Trophoblastic Neoplasia**Nonmetastatic: disease confined to the uterus****Metastatic: disease spread outside the uterus****Good Prognosis (low risk)**

Short duration: disease present <4 months
 Pretreatment hCG titer: <40,000 mIU/mL
 No previous chemotherapy

Poor Prognosis (high risk)

Long duration: disease present >4 months
 Pretreatment hCG titer: >40,000 mIU/mL
 Brain or liver metastases
 Failure of previous chemotherapy
 Disease after term pregnancy

hCG, human chorionic gonadotropin.

1. **Nonmetastatic GTT (persistent or invasive mole)** is molar tissue that invades the uterine wall, produces persistent hCG elevation, and potentially causes bleeding. It is confined to the uterus and is the most common form of GTT.
2. **Metastatic disease** (disease outside the uterus) may be found most commonly in the lung (80%) and the vagina (30%), but may also affect the liver (10%) and brain (10%). Patients have various symptoms, such as **vaginal bleeding (vaginal metastasis)**, **hemoptysis (pulmonary metastases)**, or **neurologic symptoms (brain metastases)**. The disease is often associated with hemorrhage because of the propensity of trophoblastic tissue to invade vessels. Metastases are very friable, and biopsy to confirm diagnosis is not recommended. In the setting of the appropriate clinical history and an elevated hCG, lesions visualized on radiographic studies are treated presumptively.

B Diagnosis

1. **After evacuation of a molar pregnancy**, GTT is diagnosed when there is a documented increase in hCG, the value of hCG reaches a plateau for 3 weeks, or metastatic disease is identified.
2. Weeks or years **after an abortion or ectopic pregnancy**, elevated hCG may indicate GTT or another pregnancy.

C Management

1. **Workup of patients with GTT** should include the following:
 - a. Complete history and physical examination
 - b. Pretreatment hCG titer, hematologic survey, serum chemistries, and liver function studies
 - c. Pelvic ultrasound
 - d. Computed tomography (CT) scan of the abdomen and pelvis
 - e. Chest radiograph or chest CT
 - f. CT or magnetic resonance imaging of the brain in high-risk patients
2. **Nonmetastatic GTT is almost 100% curable.**
 - a. **Single-agent chemotherapy** cures more than 90% of patients. Hysterectomy may be offered to decrease the number of treatments required for the patient who does not desire future fertility.
 - (1) **Methotrexate** is the most commonly used treatment agent. This **antimetabolite** inhibits purine synthesis by blocking the dihydrofolate reductase enzyme required to process folic acid. This results in arrested synthesis of DNA, RNA, and proteins.
 - (a) **Common side effects** include ulcerations of the mouth and gastrointestinal tract mucosa, as well as nausea. **Less common side effects**, seen when multiple or high doses are used, include myelosuppression, hepatotoxicity, nephrotoxicity, alopecia, and pneumonitis.
 - (b) **Leucovorin** (folinic acid) is administered 24 hours after each methotrexate dose to rescue normal cells from methotrexate toxicity.
 - (c) Folic acid should be avoided during methotrexate treatment as it interferes with the action of the methotrexate.

- (2) **Actinomycin D** is an **antibiotic** that intercalates DNA strands. It is also an effective single-agent treatment for nonmetastatic GTT.
- (3) **Failure** of single-agent treatment is rare. Most patients are still curable by switching to another agent or switching to a multidrug regimen.
- b. Follow-up**
 - (1) hCG titers should be followed carefully: weekly until normal for 3 weeks, then monthly until normal for 12 months.
 - (2) Contraception, preferably with oral contraceptives or medroxyprogesterone (Depo-Provera), should be used for 12 months to allow accurate monitoring of posttreatment hCG levels and to avoid misinterpretation of rising hCG levels due to normal pregnancy.
- 3. Metastatic GTT**
 - a. Good-prognosis metastatic GTT** (see Table 39–3)
 - (1) The following factors are associated with a **good prognosis**:
 - (a) Short duration of disease (less than 4 months)
 - (b) Low pretreatment hCG titer (less than 40,000 mIU/mL)
 - (c) No metastatic spread to the brain or liver
 - (d) No previous chemotherapy
 - (2) **Single-agent chemotherapy** with methotrexate or actinomycin D can be used to treat good-prognosis metastatic GTT. However, more courses of chemotherapy are usually required, and alternative therapy is needed more frequently than in nonmetastatic GTT.
 - (3) **Follow-up** is similar to that for nonmetastatic GTT (see III C 2 b).
 - b. Poor-prognosis metastatic GTT**
 - (1) The following factors are **associated with a poor prognosis**:
 - (a) Long duration of disease (more than 4 months)
 - (b) High pretreatment hCG titer (more than 40,000 mIU/mL)
 - (c) Liver or brain metastases
 - (d) Failure of previous chemotherapy
 - (e) Disease after a term pregnancy
 - (2) **Treatment**
 - (a) Affected patients are treated with **multiagent chemotherapy** such as EMA-CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine [Oncovin]) and a multiple modality approach (i.e., chemotherapy, surgery, and radiation).
 - (b) High-risk patients should be treated in centers that have a special interest and expertise in this disease, especially when life-threatening toxicity from therapy is a factor.
 - (c) The survival rate is approximately 80%.
 - (d) Hysterectomy usually does not improve the outcome.
 - (3) **Follow-up**
 - (a) Three additional courses of chemotherapy after a negative hCG titer
 - (b) Monitoring of hCG levels weekly until negative for 3 weeks, then monthly for 24 months) due to the increased risk of late recurrence
 - (c) Contraception for at least 24 months after negative levels of hCG

D Recurrence rates

- 1. Nonmetastatic GTT: 1%
- 2. Good-prognosis metastatic GTT: 5%
- 3. Poor-prognosis metastatic GTT: up to 20%

E Future fertility Fertility after chemotherapy for GTT is usually retained since the chemotherapy agents used do not deplete the oocytes in the ovary. Women who choose to become pregnant should be monitored carefully. A normal intrauterine pregnancy should be documented in the first trimester, the placenta should be histologically evaluated after delivery, and hCG titers should be followed to zero postpartum.



Study Questions for Chapter 39

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

Questions 1 and 2 are based on the clinical scenario described below.

A 20-year-old, gravida 2, para 1, at 22 weeks of gestation by her last menstrual period presents to the emergency department complaining of heavy, painless vaginal bleeding. She has had no prior prenatal care. Her vital signs are: T = 98.3°F, HR = 110, BP = 120/85, RR = 18. On physical examination, you note a fundal height of 24 cm, and there are no fetal heart tones on auscultation. Speculum examination reveals bright red blood filling the vagina. The cervix is closed and long. Laboratory studies reveal a quantitative hCG of 110,000 mIU/mL. Imaging studies are pending.

1. What are the most likely findings to be revealed on pelvic ultrasound?
 - ☐ A Single, live, intrauterine pregnancy at approximately 24 weeks' gestation
 - ☐ B Complete placenta previa
 - ☐ C Uniformly hydropic villi
 - ☐ D Presence of fetal parts, as well as focal trophoblastic proliferation
 - ☐ E Small ovaries, bilaterally, with a 6-cm corpus luteum cyst on the left ovary

2. Following suction dilation and curettage, cytogenetic analysis is performed on the tissue. What is the most likely karyotypic finding?
 - ☐ A Maternal 0 + Paternal X (duplicated)
 - ☐ B Maternal 0 + Paternal X + Paternal Y
 - ☐ C Maternal X + Paternal X + Paternal X
 - ☐ D Maternal X + Paternal X + Paternal Y
 - ☐ E Maternal X + Paternal Y + Paternal Y

3. A 29-year-old, gravida 2, para 0, at 19 weeks by last menstrual period, presents to the emergency department complaining of heavy vaginal bleeding. She is hemodynamically stable. Physical examination reveals a fundal height of 28 cm, and bright red blood in the vagina, with a closed cervix. Quantitative hCG is 190,000 mIU/mL. Ultrasound reveals absence of fetal tissue, diffuse, hydropic villi, and bilaterally enlarged ovaries with multiple, large, theca lutein cysts. What is the preferred management of this condition?
 - ☐ A Bilateral ovarian cystectomies, with ovarian fixation
 - ☐ B Dilation and suction curettage, with concurrent bilateral ovarian cystectomies
 - ☐ C Total abdominal hysterectomy and bilateral salpingo-oophorectomy
 - ☐ D Dilation and suction curettage, under ultrasound guidance

Questions 4 and 5 are based on the clinical scenario described below.

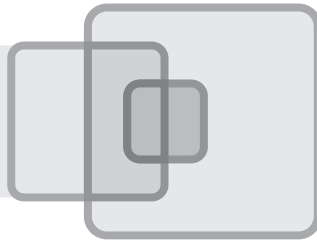
A 33-year-old, gravida 3, para 2, presents to the emergency department complaining of right upper quadrant pain. She is status post a pregnancy that resulted in spontaneous abortion 6 months ago, and reports intermittent vaginal spotting since that time. Her vital signs are T = 98.6°F, HR = 92, BP = 110/70, RR = 16. Laboratory studies reveal a quantitative hCG of 90,000 mIU/mL and hemoglobin 10.8 mg/dL. Physical examination reveals tenderness in the right upper quadrant of the abdomen without rebound or guarding. Pelvic examination reveals a 16-week sized, globular, nontender uterus with minimal bleeding at the cervical os. CT of the abdomen reveals multiple masses in the liver.

4. Which of the following treatments is most appropriate?
- ☐ A Actinomycin D
 - ☐ B Dilation and suction curettage
 - ☐ C Single-agent chemotherapy with methotrexate
 - ☐ D Hysterectomy
 - ☐ E Multiagent chemotherapy with etoposide, methotrexate, actinomycin D, cyclophosphamide and vincristine (EMA-CO)
5. Following completion of treatment, what is the most appropriate follow-up for this patient?
- ☐ A One additional course of chemotherapy after negative hCG
 - ☐ B Serial hCG measurements: monthly until normal for 6 months
 - ☐ C Depot medroxyprogesterone
 - ☐ D Serial chest radiographs



Answers and Explanations

- 1. The answer is C.** The case presentation is most consistent with a complete molar pregnancy, because the uterus is larger than would be expected by last menstrual period, and because of the quantitative hCG greater than 100,000. The typical appearance of a complete mole on ultrasound includes the presence of uniformly hydropic villi (C). A single, live intrauterine pregnancy at 24 weeks' gestation would not account for the exceedingly high hCG level. A complete placenta previa would not be associated with size greater than dates, or with the high hCG level. The presence of fetal parts as well as focally abnormal trophoblastic tissue is associated with a partial or incomplete mole. The ovaries in a patient with a complete mole are likely to be bilaterally enlarged with theca lutein cysts.
- 2. The answer is A.** In most cases of complete mole (90%), an "empty" ovum is fertilized by a single sperm, which duplicates its DNA. This results in an abnormal 46,XX karyotype. Complete molar pregnancies can also be caused by an "empty" ovum being fertilized by two sperm, resulting in an abnormal 46,XX or 46,XY karyotype, but this is far less common (10%). The remaining answer choices are all possible karyotypes in an incomplete, or partial mole.
- 3. The answer is D.** The clinical scenario is consistent with complete molar pregnancy, because of the hCG greater than 100,000, the enlarged uterine size compared to reported gestational age, and the ultrasound findings. The patient has no clinical evidence of ovarian torsion at this time. The preferred management of complete molar pregnancy is dilation and suction curettage, under ultrasound guidance. Even large theca lutein cysts associated with complete molar pregnancy will resolve as hCG levels drop. Therefore, in the absence of clinical emergency, there is no indication for ovarian cystectomies or fixation. Hysterectomy and bilateral salpingo-oophorectomy is not indicated in this patient of childbearing age.
- 4. The answer is E.** This patient has poor-prognosis, metastatic GTT, with metastases to the liver. The following factors contribute to her poor prognosis: more than 4 months since preceding pregnancy, high hCG (greater than 40,000 mIU/mL), and metastasis to the liver. Therefore, the best treatment for her is multiagent chemotherapy in a center with particular expertise in this disease. Actinomycin D or methotrexate alone is indicated for treatment of good-prognosis, metastatic GTT. Dilation and curettage may be indicated to clear residual disease from within the uterine cavity, but will not adequately treat the metastatic disease. Hysterectomy does not improve outcome in patients with poor-prognosis, metastatic GTT.
- 5. The answer is C.** The most important step following treatment of any molar pregnancy is to ensure that the patient does not get pregnant again within the 24 months, so as not to confound follow-up with hCG levels. In patients with poor-prognosis, metastatic GTT, three additional courses of chemotherapy after normalization of hCG levels are indicated. Serial hCG should be checked weekly until normal for 3 weeks, then monthly until normal for 24 months. Serial chest radiographs to evaluate for chest metastases are not warranted in this patient.



Pelvic Malignancies

ANDREA R. HAGEMANN • CHRISTINA S. CHU

I

CERVICAL CANCER

Cervical cancer is the most preventable gynecologic cancer because of the Pap test. George Papanicolaou developed a method of identifying abnormal cells in exfoliative cytology in the 1920s and published his work in the 1940s. Pap test screening is now an integral part of health care in the United States. In some developing countries, where Pap smears are not routinely performed, cervical cancer remains the most common cause of cancer death in women.

A Epidemiology and etiology

1. **Frequency peaks** between 45 and 60 years of age.
2. In the United States in 2009, it was estimated that 11,270 cases of cervical cancer would be diagnosed, with approximately 4,000 deaths anticipated due to cervical cancer. This is in contrast to a worldwide incidence of approximately 500,000 cases of cervical cancer, and 250,000 attributed deaths in the same year.
3. **Increased incidence** is related to:
 - a. First intercourse at a young age
 - b. Marriage or conception at a young age
 - c. Multiple sexual partners
 - d. Cigarette smoking. By-products of cigarette smoke are concentrated in cervical mucus and have been associated with a depletion of the cells of Langerhans, which are macrophages that assist in cell-mediated immunity
 - e. High-risk sexual partners (e.g., those whose previous sexual partners developed precancerous or cancerous conditions of the cervix or penis)
 - f. Immunosuppression (e.g., from HIV infection or medications to maintain immunosuppression for organ transplantation)
 - g. In utero diethylstilbestrol (DES) exposure
4. **Infectious associations**
 - a. **Human papilloma virus (HPV)**, a nonenveloped double-stranded DNA virus, is responsible for the vast majority of cases of cervical cancer. Incorporation of the E6 and E7 open reading frames into the cervical cell genome is associated with progression to invasive disease.
 - (1) There are over 100 types of the HPV virus. Not all are associated with cervical cancer.
 - (2) HPV is detected in more than 95% of cervical cancers and precancers. It is also detected in 50% of vaginal cancers/precancers, over 50% of vulvar cancers/precancers, 50% of penile cancers, and over 70% of anal cancers.
 - (3) About 30 to 40 types of HPV are associated with anogenital infection.
 - (4) Of these, about 15 to 20 types are considered oncogenic, and include types 16, 18, 31, 33, 35, 39, 45, 51, 52, and 58.
 - (5) Nononcogenic types include types 6, 11, 40, 42, 43, 44, and 54. Of these, types 6 and 11 are most often associated with genital warts.
 - (6) By the age of 50 years, at least 80% of women in the United States will have acquired a genital HPV infection. Among women younger than the age of 25, the prevalence is as high as 46%.
 - (7) Fortunately, about 70% to 80% of HPV infections are transient and cleared by the immune system within 1 to 2 years.

- b. **Herpes simplex virus-2 (HSV-2).** HSV-2 DNA and messenger RNA sequences have been found in cervical cancer cells and may increase the likelihood of HPV infection.

B Preinvasive cervical disease

1. **Pap test screening.** The **cervical transformation zone (TZ)** is the site of most **squamous preinvasive and invasive neoplasms**. The TZ undergoes a transformation from mucus-secreting glandular cells to non-mucus-secreting squamous cells in a normal process called **metaplasia** (change in growth). **Active metaplasia** is most susceptible to infection by HPV.

a. Types of Pap smears

- (1) A **traditional Pap smear** is performed using a wooden spatula to wipe cells from the surface of the cervix and a brush to wipe cells from the endocervical canal. The cells are smeared onto a slide that is fixed and stained for cytologic evaluation. This is less commonly performed since the advent of liquid cytology methods.
- (2) A **liquid cytology** method (e.g., Thin Prep, AutoCyte) is used to create a Pap test that is easier to evaluate. This test has largely replaced the traditional Pap smear. The specimen is collected by wiping cells from the cervix and endocervix. The cells are then suspended in liquid, which is processed to remove blood, mucus, and debris. The remaining concentrated suspension of cells is used to create a stained slide for evaluation. The specimens collected in this fashion can also be used to identify HPV subtypes, providing information that may help assess risk in a patient with a progressing lesion.

b. Efficacy of cytologic screening programs

- (1) **Invasive carcinoma of the cervix** is usually preceded by a spectrum of **preinvasive disease**, which can be detected cytologically (e.g., with the Pap test). Detection and simple local treatments of preinvasive cervical disease can prevent invasive cancer.
- (2) **Regular cervical cancer screening programs** have demonstrated a significant decrease in mortality from cervical cancer. Unscreened populations can have as high as a tenfold or greater increase in mortality from cervical cancer.

c. Frequency of cervical cytologic screening

- (1) **The American Congress of Obstetricians and Gynecologists 2009 recommendations** state that screening should be initiated at the age of 21 years. Cervical cancer is very rare in younger women (1 in 1,000,000), and screening has been unsuccessful in preventing these rare cancers. As such, overtreatment of younger individuals should be avoided. Up to age 30, women should undergo Pap testing every 2 years since young women are at elevated risk for acquiring high-risk HPV subtypes that predispose to high-grade dysplasia.
- (2) Women with high-risk factors (see IA 3) should be screened annually.
- (3) Low-risk women older than the age of 30 years have two options:
 - (a) Patients with three negative consecutive paps may be screened every 3 years with a pap, or
 - (b) Women may undergo pap and HPV testing. Patients with negative pap and negative screening for high-risk subtypes of HPV may forgo screening for 3 years.
- (4) Women older than the age of 70 years with three or more normal Pap tests in a row in the previous decade may consider discontinuation of Pap testing at the discretion of the physician.
- (5) Women who have had a total abdominal hysterectomy (with removal of the cervix) and no history of cervical cancer or dysplasia may discontinue Pap test screening. Patients who have had CIN2 or 3 need yearly paps for 3 years and then should continue to be screened even after their period of posttreatment surveillance.

d. Evaluation of the abnormal Pap test. The **Bethesda system** uses descriptive terms that correlate with histology. This analysis includes:

- (1) A statement regarding the adequacy of the sample
- (2) A general categorization statement (optional)
- (3) A descriptive diagnosis regarding benign or reactive changes, low- or high-grade intra-epithelial lesions (LSILs or HSILs), glandular cell abnormalities, or the presence of malignant cells

2. **Further diagnosis with colposcopy.** The Pap test is a screening test and as such carries a false-negative rate of 15% to 40% for invasive cancers. Colposcopy provides a more definitive diagnosis. This technique involves using magnification to inspect the TZ after applying a 3% to 5% acetic acid solution. Biopsies are performed of abnormal-appearing epithelium. Colposcopically directed biopsies carry an accuracy of 85% to 95%. **Endocervical curettage** is performed in conjunction with colposcopy to rule out dysplasia within the canal that is not visualized.
3. **Treatment.** Therapeutic recommendations are based on colposcopic biopsy.
 - a. **Low-grade lesions** can be treated surgically or followed conservatively. Although there is a 70% incidence of regression, there is a 15% incidence of progression to a high-grade abnormality.
 - b. **Destruction or excision of the TZ** may be performed using the following methods:
 - (1) **Cold-knife conization (CKC)** is the gold standard because a pathologic specimen with clean margins is obtained. This procedure is performed in the operating room under general or regional anesthesia using a scalpel. It is recommended in the following circumstances:
 - (a) Significant dysplastic lesions with either a nonvisualized component or a positive endocervical canal curettage
 - (b) High-grade lesions that do not correlate with colposcopic findings
 - (c) Premalignant or malignant glandular cell abnormalities
 - (2) **Loop excision** is commonly called a loop electrosurgical excision procedure (LEEP) or large loop excision of transformation zone (LLETZ). This procedure is easily performed in the office with local anesthesia. A hot metal loop is used to excise a wedge of cervical tissue. Disadvantages include a cautery artifact at the margin of the specimen and a limited biopsy size because of lack of general anesthesia or size of the metal loop.
 - (3) **Cryotherapy** involves freezing the cervix in the office. It has the disadvantages of yielding no tissue for pathologic evaluation and potential scarring and is less commonly performed.
 - (4) **Laser vaporization or laser conization** is also performed at some centers, but like cryotherapy, is performed less frequently.
 - c. **Cure rates** for preinvasive disease after one treatment range from 85% to 95%. Repeat treatment of the adequately evaluated persistent lesion results in a cure rate of 95%.
 - d. The risk of premalignant lesions persisting or recurring is 5% to 15%. Of these lesions, 85% are detected within 2 years of the initial treatment. **Follow-up** should follow the American Society for Colposcopy and Cervical Pathology guidelines and include:
 - (1) Cytologic evaluation every 3 to 6 months for the first year posttreatment
 - (2) Repeat colposcopic evaluation for persistent or recurrent abnormalities
 - (3) Hysterectomy for patients who have persistent severe lesions despite repeated conservative local destructive techniques

C Microinvasive carcinoma of the cervix Much controversy surrounds the exact definition of “early” invasive cancer of the cervix. A commonly adopted definition in the United States is a depth of invasion less than or equal to 3 mm, lesion width of less than or equal to 7 mm, and no evidence of lymphatic or vascular space involvement.

1. **Diagnosis** can be made only by means of a thoroughly examined cone biopsy specimen.
2. The **incidence of pelvic lymph node metastases** is less than 4%.
3. The treatment of choice is **total abdominal hysterectomy**, although cervical conization with negative margins may be used in women who wish to preserve fertility.
4. The **cure rate** is 95%.

D Invasive carcinoma of the cervix

1. **Symptoms**
 - a. Postcoital or irregular bleeding is the most common symptom.
 - b. Malodorous, bloody discharge; sciatica; leg edema; and deep pelvic pain are seen in advanced disease.

TABLE 40–1 Staging System for Cervical Cancer

Stage I: Carcinoma is confined to cervix
Stage IA: Invasive cancer which is diagnosed only by microscopy; tumors ≤ 5 mm deep or ≤ 7 mm wide
Stage IA1: Invasion ≤ 3 mm in depth and ≤ 7 mm in width
Stage IA2: Invasion > 3 mm and ≤ 5 mm in depth, and ≤ 7 mm in width
Stage IB: All other cases of stage I
Stage IB1: Clinically visible lesion ≤ 4 cm in greatest dimension
Stage IB2: Clinically visible lesion > 4 cm in greatest dimension
Stage II: Carcinoma extends beyond cervix but not onto pelvic sidewall or to the lower third of the vagina
Stage IIA: No obvious parametrial involvement
Stage IIA1: Clinically visible lesion ≤ 4 cm in greatest dimension
Stage IIA2: Clinically visible lesion > 4 cm in greatest dimension
Stage IIB: Obvious parametrial involvement
Stage III: Carcinoma extends to pelvic sidewall. On rectal examination, there is no cancer-free space between tumor and pelvic sidewall. Tumor extends to lower third of vagina. All cases of hydronephrosis and nonfunctioning kidney should be included in stage III diagnoses unless another cause for these conditions can be found
Stage IIIA: Tumor extends to lower third of vagina, with no extension to pelvic sidewall
Stage IIIB: Extension onto pelvic sidewall, hydronephrosis, or nonfunctioning kidney
Stage IV: Carcinoma extends beyond true pelvis or clinically involves mucosa of bladder or rectum
Stage IVA: Spread to mucosa of bladder or rectum
Stage IVB: Spread beyond true pelvis

2. **Histology.** Squamous carcinomas (80%) and adenocarcinoma (15%) account for most invasive cervical cancer. There appears to be no difference in survival rates between women with these two groups of cancer when the lesions are matched for grade, size, and stage. Adenocarcinomas are glandular lesions, and tend to be multifocal (with so-called “skip lesions”), so clear and precise margins are essential when considering conservative therapy. Rare tumors of the cervix include small cell/neuroendocrine carcinomas, sarcomas, and lymphomas.
3. **Staging** (Table 40–1). Staging is **clinical** and does not change after surgery. Assessment for staging is based on cervical biopsies, physical examination, radiologic imaging of the kidneys and ureters to identify hydronephrosis caused by tumor extension, proctoscopy, cystoscopy, and chest radiography. Computed tomography (CT), MRI or PET/CT may be used to identify metastases and more appropriately develop a treatment plan, but again these results do not change the stage. The purpose of clinical staging is to use techniques available worldwide and avoid understaging, as most cases of cervical cancer occur in developing countries.
4. **Treatment.** Therapeutic measures are governed by the patient’s age and general health and by the clinical stage of the cancer. Primary modalities include surgery and radiotherapy. Chemotherapy is commonly used as a radiation sensitizer.
 - a. **Surgery.** This modality may be considered for patients with stage I or IIA disease. Typically, a **radical hysterectomy** with para-aortic and pelvic lymphadenectomy is performed. This procedure involves en bloc removal of the uterus, cervix, upper third of the vagina, parametrium, and uterosacral and uterovesical ligaments. In addition, the lymphatic nodes of the lower para-aortic, common iliac, and pelvic regions are removed en bloc. Very select cases may be treated with **radical trachelectomy** (radical removal of the cervix, upper vagina, and parametria) in order to preserve fertility. This procedure may be considered in carefully selected women with small tumors (stages IA2 to IB1) who strongly desire to retain the ability to attempt childbearing. A permanent cerclage must be placed at the time of the procedure to maintain competence of the lower uterine segment during pregnancy.
 - (1) **Comparable cure rates** between surgery and radiotherapy are the rule in the treatment of early-stage disease. The best treatment of very bulky cervical cancers, which appear to be limited to the cervix, is still debated, but will usually be multimodal.
 - (2) The **ovaries may be preserved with** surgical treatment, allowing for continued hormonal function in premenopausal women.

- (3) **Five-year survival rates with surgery** alone range from 75% to 100% for stages IA and IIA patients, depending on operative findings. Postoperative radiation with or without chemotherapy may improve survival in some cases.
- b. **Radiotherapy.** This treatment modality may be used for **all stages of cervical cancer**, either for curative or palliative intent. A series of randomized trials in the 1990s solidified the role of **chemotherapy** as an effective radiation **sensitizer**, meaning it improves the success of the radiation. Currently, chemotherapy, usually weekly intravenous cisplatin, is **included in most situations in which radiation therapy is used**.
 - (1) Primary treatment usually involves **external beam radiotherapy (EBRT)** to the pelvis followed by intracavitary treatment or **brachytherapy**.
 - (2) EBRT may be extended to include the para-aortic lymph nodes if they are involved or are at high risk for occult involvement.
 - (3) Radiotherapy may be administered **after radical hysterectomy** for high-risk patients, including those with positive surgical margins, lymph–vascular space involvement, and disease within lymph nodes.
 - (4) **Five-year survival rates with radiotherapy alone** are comparable for survival with surgery alone for stages IA and IIA disease.
 - (5) For advanced-stage disease localized to the pelvis, 5-year survival varies from 50% to 80%. For metastatic disease out of the pelvis, survival is less than 15%.
5. **Follow-up.** Approximately 35% of patients with invasive cervical cancer are estimated to have persistent or recurrent disease. Most of these (85%) have a recurrence of disease within 3 years of the initial treatment.
 - a. **Frequent checkups** are mandatory in the first 3 years. Evaluations include pelvic examinations, careful palpation of nodal groups, Pap smears, and radiologic imaging.
 - b. **Suspicious signs and symptoms** include a persistent cervical or vaginal mass, unilateral leg edema, hydronephrosis, pelvic or sciatic pain, vaginal discharge, and palpable supraclavicular or groin nodes.
6. **Treatment of recurrent disease.** Treatment depends on whether recurrent disease is confined to the pelvis or is distant.
 - a. **Pelvic confined**
 - (1) Of **patients treated primarily with surgery**, 25% are saved after recurrence of the disease with pelvic radiotherapy.
 - (2) In **patients treated primarily by radiotherapy** and in whom extensive presurgical and intraoperative evaluations reveal no evidence of metastatic tumor, partial or total **pelvic exenteration** (e.g., en bloc removal of the uterus, cervix, vagina, parametrium, bladder, and rectum) is appropriate. This surgery often involves colostomy, urinary diversion, and vaginal reconstruction, and may be curative in up to 70% of cases.
 - b. **Distant recurrence.** These patients are usually treated with chemotherapy. Cures are exceedingly rare, and response rates are variable and of limited duration. Radiotherapy can be used for the palliation of painful metastases.

E Prevention of cervical cancer

1. **Secondary prevention** of cancer involves detection of dysplastic lesions (i.e., by Pap testing and colposcopy) and then intervention to treat the precancerous areas before they become cancer.
2. **Primary prevention** of cervical cancer focuses on prevention of HPV infection.
 - a. Two HPV vaccines are currently approved by the Food and Drug Administration (FDA) for the prevention of HPV infection.
 - b. Gardasil® is a quadrivalent vaccine that covers HPV types 6, 11, 16, and 18. HPV 16 and 18 account for 70% of all cervical cancers, adenocarcinoma in situ, severe cervical dysplasia (CIN3), and moderate and severe vulvar and vaginal dysplasia. HPV 16 and 18 are also responsible for 50% of moderate cervical dysplasia (CIN2). Together, these four types are responsible for 90% of cases of genital warts. This vaccine is currently approved for girls and young women ages 9 to 26, though additional data are being collected on its effectiveness in women of older ages. The vaccine is not FDA-approved for males.

- c. Cervarix® covers HPV types 16 and 18, and may offer some protection against types 31, 33, and 45. It is currently approved for women ages 10 to 25.
- d. The approved vaccines appear to be 93% to 95% effective in preventing HPV 16- and 18-related cervical cancer.
- e. The vaccines are effective at preventing primary infection with the types of HPV virus included, but do not appear to be effective treatment for preexisting infections. An individual who has been infected with one of the included types may still benefit and develop immunity to the other strains included in the vaccines and therefore should still be vaccinated if appropriate.

II

ENDOMETRIAL CANCER

This disease is the most common gynecologic malignancy and the most curable.

A Epidemiology

1. **Incidence.** Endometrial cancer will eventually affect 2% to 3% of women in the United States. In 2009, it was estimated that approximately 42,000 new cases of endometrial cancer would be diagnosed, with approximately 7,700 attributed deaths.
2. **Risk factors.** Increased risk of endometrial cancer has been associated with factors related to prolonged or increased estrogen exposure without the controlling effects of adequate progestin or progesterone. Conditions associated with excess estrogen include:
 - a. **Early menarche**
 - b. **Late menopause**
 - c. **Obesity** resulting in increased conversion of androstenedione to estrone in fat cells. Women who are more than 50 lb overweight have a ten times higher risk of developing endometrial cancer over normal-weight individuals.
 - d. **Polycystic ovary syndrome (PCOS) with chronic anovulation** is associated with production of estrogen with a lack of progesterone production. Ovulation is suppressed by a complex mechanism involving androgens and insulin in the ovary. As a result, production of progesterone (a potent “antiestrogenic” hormone) is suppressed, leaving the endometrium exposed to “unopposed” estrogen. Unopposed stimulation of the endometrium by estrogen leads to endometrial hyperplasia (a premalignant lesion) and endometrial carcinoma. In addition, obesity increases peripheral conversion of androgens to estrogens in fat thereby increasing the amount of estrogen available to stimulate the endometrium in these women. Since over 50% of women with PCOS are obese, this is another significant mechanism increasing the risk of endometrial cancer in women with PCOS.
 - e. **Exogenous unopposed estrogen.** A significant correlation exists between use of exogenous estrogen and endometrial cancer when estrogen therapy is administered without the protective effects of a progestin.
 - f. **Tamoxifen.** This agent acts as an antiestrogen in the breast but stimulates the endometrium similarly to estrogen, resulting in an increased risk of endometrial cancer (relative risk of 7). The therapeutic benefit in appropriately selected women with breast cancer outweighs this risk.
 - g. **Estrogen-secreting tumors.** Granulosa and theca cell ovarian tumors produce active estrogen and have been associated with a 25% incidence of a concurrent endometrial carcinoma.
 - h. **Other factors.** A history of breast and ovarian cancers is associated with an increased risk of a concomitant endometrial carcinoma. In addition, a history of hypertension and diabetes mellitus is associated with an increased risk of endometrial carcinoma, although these factors may be related to obesity.
3. The **Lynch syndrome**, also called **hereditary nonpolyposis colorectal cancer syndrome**, is an autosomal dominant-inherited predisposition to developing cancer. Mutations in MLH1, MSH2, and MSH6, genes essential for proper DNA mismatch repair, lead to microsatellite instability and the increased risk of cancer in these individuals. Endometrial cancer is the second most common cancer in women of Lynch families. It is recommended that affected women consider prophylactic hysterectomy when childbearing is complete.

4. Factors associated with **decreased risk** are smoking, high parity, and use of oral contraceptives. Endometrial cancer that occurs in the absence of estrogenic risk factors is rare and often has a worse prognosis with more aggressive cell types and early metastases.

B Endometrial hyperplasia, which may be a precursor to endometrial carcinoma

1. **Types of endometrial hyperplasia** are classified on the basis of the extent of endometrial gland crowding and on cellular atypia.
 - a. **Simple hyperplasia** without atypia is associated with a 1% risk of progression to cancer. For simple hyperplasia with atypia, the risk is 8%.
 - b. **Complex hyperplasia** without atypia is associated with a 3% risk of progression to cancer. For complex hyperplasia **with atypia, the risk is 29%**.
2. The **diagnosis of endometrial hyperplasia** must be established with adequate sampling of the endometrium in any woman with abnormal bleeding who is older than 35 years of age. Sampling modalities include office endometrial biopsy or dilation and curettage (D&C) performed in the operating room under anesthesia. Endometrial biopsy is the preferred modality for most women as it is 99% accurate and easily performed in an office setting.
3. **Treatment of endometrial hyperplasia**
 - a. **Young women desiring fertility** may be treated with 3 to 6 months of progestin therapy, followed by a repeat endometrial sampling.
 - b. Proper sampling of the endometrium of **perimenopausal and postmenopausal women** with D&C to ensure proper diagnosis is essential.
 - (1) For hyperplasia without atypia, initial treatment is **conservative**: 3 to 6 months of progestin therapy followed by a repeat endometrial sampling.
 - (2) **Hysterectomy** is recommended for women with complex atypical hyperplasia and for women with persistent hyperplasia after treatment with a progestational agent.

C Endometrial carcinoma

1. **Symptoms.** The most common symptom of endometrial carcinoma is irregular menses or postmenopausal bleeding. Any woman older than 35 years of age with heavy menses or bleeding throughout the month should have an endometrial biopsy.
2. **Age.** The median age for endometrial cancer is 61 years. The largest number of patients is between 50 and 59 years of age.
3. **Histology**
 - a. The **principal histologic subtype** of endometrial carcinoma is **endometrioid adenocarcinoma** (75% to 85%). This is often referred to as Type 1 endometrial cancer, associated with the risk factors listed above. The remaining subtypes include mucinous, papillary serous, clear cell, and squamous carcinoma. Histologic differentiation correlates with depth of myometrial penetration, pelvic and periaortic lymphatic metastases, and overall 5-year survival.
 - b. **Papillary serous and clear cell** subtypes are often referred to as Type 2 endometrial cancers. They are associated with a lower survival rate, and typically are not associated with excess estrogen stimulation or endometrial hyperplasia. Women affected by these histologic types are usually older and multiparous, with less frequency of obesity, diabetes or hypertension.
4. **Staging** is based on surgical findings (Table 40–2).
5. **Diagnosis and staging evaluation**
 - a. **D&C.** This procedure is the definitive method of diagnosis. However, an **office biopsy** may yield a diagnosis without the additional need for a D&C.
 - b. **Preoperative workup** should include a chest radiograph. A CT scan or other imaging studies of the abdomen and pelvis are optional.
6. **Treatment.** A surgical staging evaluation includes total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic or para-aortic lymphadenectomy. Omentectomy is performed in cases of high-risk histology (such as clear cell or papillary serous). **Intraoperative evaluation** of the depth of uterine invasion may be performed by a pathologist. Sampling of **nodes from the pelvic and para-aortic regions** is recommended for patients with intermediate- or high-risk features, including poorly differentiated cancer, tumor invasion through more than

TABLE 40–2 Staging System for Endometrial Carcinoma

Stage I: Confined to uterus
Stage IA: Tumor limited to endometrium or less than one-half of the myometrium
Stage IB: Tumor invasion equal to or more than one-half of the myometrium
Stage II: Involvement of the cervical stroma, but no extension beyond the uterus
Stage III: Local and/or regional spread of the tumor
Stage IIIA: Tumor invades serosa and/or adnexa
Stage IIIB: Vaginal and/or parametrial involvement
Stage IIIC: Metastases to pelvic and/or para-aortic nodes
Stage IIIC1: Positive pelvic nodes
Stage IIIC2: Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV: Mucosal involvement of bladder or rectum, and/or distant metastases
Stage IVA: Tumor invades bladder or bowel mucosa
Stage IVB: Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

For all stages, the degree of differentiation is noted as G1, G2, and G3.

half of the uterine wall, or cervical extension of tumor. Some experts recommend sampling the lymph nodes in all cases, including those of complex atypical hyperplasia, because of the uncertainty associated with intraoperative frozen section.

- a. **Low-risk patients** comprise those with **stage IA, grade 1 or 2 carcinomas**. This group of tumors has few poor prognostic features. Surgery (total abdominal hysterectomy and bilateral salpingo-oophorectomy) alone is usually considered adequate treatment. Disease-free survival rate is 96%.
- b. **Intermediate-risk patients** are those with **grade 3 tumors, stage IB, or stage II**, with **no other extrauterine spread**. These patients may be offered pelvic irradiation, vaginal cuff irradiation, or hormonal therapy. Patients with full surgical staging (negative pelvic and para-aortic lymph nodes) may also forgo adjuvant radiation therapy.
- c. **High-risk patients** include those with **adnexal spread, node metastases, deep myometrial invasion, or grade 3 tumors**. Adjuvant radiotherapy and/or chemotherapy may be beneficial.
- d. **Stage IV carcinomas**. Treatment in these patients must be individualized. In most instances, treatment programs involve surgery with adjuvant chemotherapy or hormonal therapy.
- e. **Follow-up**. Following definitive surgical staging, the most common site of recurrence is the vaginal cuff. If no postsurgical treatment is necessary, follow-up evaluation involves pelvic examination and Pap testing of the vaginal cuff, with or without abdominal imaging. Following chemotherapy or radiation treatment, abdominal imaging, in addition to pelvic examinations, is routinely employed for follow-up.
- f. **Recurrent disease**. Treatment for recurrent disease must be individualized, depending on the extent and site of recurrence, hormone receptor status, and patient's health. Treatment programs may include exenteration procedures, radiotherapy, chemotherapy, and hormonal therapy.

III

UTERINE CANCER

A Uterine carcinosarcoma

1. Uterine carcinosarcomas, historically referred to as malignant mixed müllerian tumors, are rare, account for 1.2% of uterine neoplasms. They are highly aggressive and carry a poor prognosis. They are more correctly referred to as carcinomas, because they appear to derive from a monoclonal cancer cell with sarcomatous metaplasia. Their clinical behavior, epidemiology, and risk factors behave more closely to that of endometrial cancer than to sarcomas, and they are staged according to the FIGO criteria for endometrial cancer. Diagnosis is made on the basis of histology, usually following surgery with total abdominal hysterectomy, bilateral salpingo-oophorectomy,

TABLE 40–3 Staging System for Uterine Sarcomas (Leiomyosarcomas and Endometrial Stromal Sarcomas)

Stage I: Tumor limited to uterus
Stage IA: ≤5 cm
Stage IB: >5 cm
Stage II: Tumor extends beyond uterus within the pelvis
Stage IIA: Adnexal involvement
Stage IIB: Involvement of other pelvic tissues
Stage III: Tumor invades abdominal tissues (not just protruding into the abdomen)
Stage IIIA: One site
Stage IIIB: >One site
Stage IIIC: Metastasis to pelvic and/or para-aortic lymph nodes
Stage IV
Stage IVA: Tumor invades bladder and/or rectum
Stage IVB: Distant metastasis

and staging lymphadenectomy. Carcinosarcomas have a high risk of recurring (up to 60%), warranting adjuvant treatment with either radiation or chemotherapy.

B Uterine sarcoma

1. Uterine sarcomas arise from the **smooth muscle and connective tissue** of the uterus, and again are rare tumors which generally carry a poorer prognosis stage for stage compared to endometrial cancer. They comprise 9% of all uterine malignancies. Types of uterine sarcoma include **endometrial stromal sarcoma, leiomyosarcoma, undifferentiated endometrial sarcoma, smooth muscle tumors of uncertain malignant potential (STUMP), and adenosarcoma**. If distant spread is to occur, it usually involves the lungs, so preoperative assessment should include thoracic imaging.
 - a. **Endometrial stromal sarcomas** are indolent tumors with a favorable prognosis. Standard treatment includes total abdominal hysterectomy with bilateral salpingo-oophorectomy. The role of lymphadenectomy is unclear, and there may be a role for ovarian preservation in select cases. Because these tumors often express estrogen and progesterone receptors, adjuvant treatment with progestins, gonadotropin-releasing hormone analogs, or aromatase inhibitors are often employed.
 - b. **Leiomyosarcomas and undifferentiated endometrial sarcomas** are aggressive tumors associated with a poor prognosis. Staging is assessed through total abdominal hysterectomy and bilateral salpingo-oophorectomy (Table 40–3). There is no role for lymphadenectomy in these cases. Postoperatively, adjuvant radiation therapy, and/or systemic chemotherapy with a taxane and gemcitabine may be employed.
 - c. **Smooth muscle tumors of uncertain malignant potential** are rare, and controversy exists as to how to best characterize these tumors. In general, they have a higher degree of cytologic atypia and a higher mitotic index than benign leiomyomas, but on microscopy exhibit greater than 5 but less than 10 mitoses per 10 high power fields, less than that seen in more aggressive uterine tumors.
 - d. **Adenosarcomas** are rare, mixed tumors, with a benign epithelial component and a more malignant sarcomatous, or stromal, element; they generally have a low malignant potential and more optimistic prognosis.

IV

EPITHELIAL OVARIAN CANCER

Epithelial ovarian cancer refers to cancer arising from the epithelial surface of the ovary. Epithelial ovarian cancer accounts for 90% of ovarian cancers. It is the most difficult gynecologic cancer to diagnose because symptoms are nonspecific. The remaining 10% of ovarian cancers, classified as “nonepithelial ovarian cancers,” arise from the ovarian germ cells, or sex cord and stromal cells; for a detailed description, see IV.

A Epidemiology

1. **Incidence.** The incidence begins to increase in the fifth decade and continues to increase until the eighth decade. In the United States in 2009, approximately 21,500 new cases of ovarian cancer were diagnosed, with 14,600 attributable deaths. Ovarian cancer is the **leading cause of death attributable to gynecologic cancers in the United States**. Approximately 1 in 70 women (1.7%) will contract ovarian cancer.
2. **Risk factors**
 - a. **Family history** of ovarian cancer is the strongest risk factor for the disease; however, **most ovarian cancer is not familial**.
 - (1) The risk is 4% to 5% if one relative is affected.
 - (2) The risk is 7% if two relatives are affected.
 - b. **Mutations in autosomal dominant tumor suppressor genes, BRCA1 and BRCA2**, which are located on chromosomes 17 and 13, respectively, are identified in 5% to 10% of patients with ovarian cancer.
 - (1) These genes account for most cases of familial breast and ovarian cancer, and confer an increased risk of ovarian cancer. The penetrance of the genes is variable but may confer a risk of 20% to 50%.
 - (2) Approximately 2% of Ashkenazi Jews are carriers of mutations in one of these genes. Familial breast ovarian cancer syndrome should be suspected if multiple family members have breast and ovarian cancer, if the age of onset of cancers is early, if multiple primary sites of cancer are noted in one patient, or if male breast cancer occurs in the family (likely BRCA2 mutation).
 - c. **Low parity and infertility** are risk factors associated with excess ovulation, which, in turn, may be an irritant to the ovary, increasing the propensity for cancer development.
3. Use of **oral contraceptives** is correlated with a **decreased risk** of ovarian cancer. Whether this is a marker for fertility rather than an independent protective factor is unclear. Tubal ligation and hysterectomy are also associated with a decreased risk of ovarian cancer.
4. **Preventive measures** include **prophylactic oophorectomy**, which should be offered to high-risk patients. These patients still have a 2% risk of developing primary peritoneal carcinoma, a cancer that is histologically identical to ovarian carcinoma but arises from the epithelial surfaces of the abdomen and pelvis. In women with BRCA1 or BRCA2 mutations, prophylactic oophorectomy should be strongly considered in the late 30s; it not only decreases the risk of ovarian cancer, but also decreases the risk of breast cancer.

B Diagnosis

1. Ovarian cancer usually produces **nonspecific symptoms** until the disease is advanced. In more than 70% of cases, the ovarian disease has spread beyond the pelvis before the diagnosis is made.
 - a. **Abdominal distention** caused by ascites is often the presenting complaint.
 - b. Lower abdominal pain, a pelvic mass, and weight loss are additional features.
2. **Early diagnosis of ovarian cancer** is rare, but it may be identified on bimanual pelvic examination or using radiologic imaging studies.
3. There is **no reliable screening test**.
 - a. Although **CA-125 levels** are elevated above the normal range in more than 85% of patients with advanced ovarian cancer, these levels should not be used for screening purposes because of the high number of false-negative and false-positive results. This is especially true in early disease when screening would be of most benefit.
 - b. **Pelvic ultrasound** is helpful in characterizing the size and architecture of the adnexal mass. Approximately 95% of ovarian cancers are larger than 5 cm. Multicystic and solid components and free fluid in the cul-de-sac are ultrasonic features suggestive of ovarian carcinoma. Ultrasound screening combined with CA-125 testing has not been shown to improve early detection rates, even in high-risk patients.
 - c. For lack of better strategy for screening, many physicians offer annual or biannual testing with **physical examination, CA-125, and transvaginal ultrasound to patients with a family history of ovarian cancer**.

TABLE 40–4 Staging System for Ovarian Cancer**Stage I:** Limited to ovaries**Stage IA:** Limited to one ovary; no ascites containing malignant cells; no tumor on external surface of ovary; capsule intact**Stage IB:** Limited to both ovaries; no ascites containing malignant cells; no tumor on external surface of ovary; capsule intact**Stage IC:** Tumor either stage IA or IB but with ascites containing malignant cells, tumor on surface of one or both ovaries, or rupture of tumor capsule**Stage II:** Involvement of one or both ovaries with pelvic extension**Stage IIA:** Extension or metastases to uterus or tubes or both**Stage IIB:** Extension to other pelvic tissues**Stage IIC:** Tumor either stage IIA or IIB but with ascites containing malignant cells, tumor on surface of one or both ovaries, or rupture of tumor capsule**Stage III:** Involvement of one or both ovaries with peritoneal metastases outside pelvis or superficial liver metastases or retroperitoneal nodes containing cancer**Stage IIIA:** Tumor limited to pelvis with negative nodes but microscopic seeding of peritoneum**Stage IIIB:** Peritoneal implants ≤ 2 cm in diameter with negative nodes**Stage IIIC:** Implants > 2 cm in diameter or positive retroperitoneal or inguinal nodes**Stage IV:** Involvement of one or both ovaries with distant metastases; this can include positive pleural effusion and intrahepatic metastases

4. **Abdominopelvic CT scan, barium enema, and chest radiography** are helpful in the evaluation of disease in women suspected of having ovarian cancer.

C Staging Surgical findings are used to stage ovarian cancer (Table 40–4). More than 60% of patients have stage III or IV disease at the time of diagnosis.

D Predominant histologic types

1. **Serous** tumors account for 40% of ovarian carcinomas.
2. **Mucinous** tumors account for 10% of ovarian carcinomas.
3. **Endometrioid tumors** account for 10% of ovarian carcinomas.
4. **Clear cell carcinoma**, which is more common in Asia, accounts for 6% of ovarian carcinomas. These cancers appear to be more resistant to chemotherapy than serous, mucinous, and endometrioid ovarian carcinomas.
5. **Small cell ovarian cancers** are rare and have a poor prognosis.
6. **Borderline ovarian tumors (also called “ovarian carcinoma of low malignant potential”)** account for 15% of epithelial malignancies. This distinct type of ovarian carcinoma has the potential to metastasize but not to invade tissues. The cell type may be papillary serous or mucinous. With surgical debulking, most of these cancers are curable. The average age at diagnosis is 48 years. Patients with these tumors have higher survival rates, and most are diagnosed in stage I.

E Clinical course of ovarian carcinoma

1. The **initial spread** of ovarian carcinoma is to adjacent peritoneal surfaces, omentum, and retroperitoneal lymph nodes.
2. **Extra-abdominal and intrahepatic metastases** occur late in the disease and only in a small percentage of cases. Stage IV cancer presents not uncommonly with a symptomatic malignant pleural effusion.
3. **Bowel obstruction** occurs as a terminal event and results from massive serosal involvement.

F Treatment A combination of surgery and chemotherapy is necessary.

1. **Goals of surgery** are to determine the extent of the disease through **staging** and to remove or **debulk** as much tumor as possible. Surgery may include the following:

- a. Exploratory laparotomy through a vertical abdominal incision, allowing a thorough evaluation of the upper abdomen
 - b. Peritoneal washings from the pelvis and upper abdomen
 - c. Inspection of all peritoneal and diaphragmatic surfaces
 - d. Excision of pelvic and para-aortic lymph nodes
 - e. Omentectomy
 - f. Debulking tumor with the goal of leaving behind as little residual disease as possible
2. **Ovarian cancer is extremely sensitive to chemotherapy.** However, this cancer has a tendency to recur.
- a. **Taxane** (such as paclitaxel or docetaxel) and **platinum** (such as carboplatin or cisplatin) chemotherapy are currently the standard treatment for all patients with ovarian cancer who have a tumor of stage IB or greater. Patients with stage IA grade 1 or 2 cancers may forgo chemotherapy. Patients with advanced disease that has been optimally debulked may benefit from a combination of intraperitoneal and intravenous chemotherapy.
 - b. **Side effects of paclitaxel** include neuropathy, alopecia, myelosuppression, hypersensitivity reaction, and bradycardia.
 - c. **Side effects of carboplatin** include nausea and vomiting, myelosuppression, and constipation.

G Recurrent ovarian cancer Although 70% of ovarian cancer responds to initial surgery and chemotherapy, most patients recur. Recurrent ovarian cancer can only very rarely be cured. Treatment is mainly palliative and usually consists of treatment with chemotherapy. Occasionally, patients may benefit from additional debulking surgery. With time, ovarian cancer develops chemotherapy resistance. Because advanced ovarian cancer usually recurs and 5-year survival in stage III disease is only 20%, patients should be encouraged to enroll in clinical trials using novel treatments.

H Fallopian tube cancer Epithelial fallopian tube cancer is very rare, accounting for 0.2% to 0.5% of all primary female genital tract malignancies. However, the true incidence may be substantially underestimated. A current hypothesis exists that papillary serous tumors of the ovary may arise from the epithelial lining of the fallopian tube fimbria. Nevertheless, this tumor behaves almost identically to ovarian cancer, and is diagnosed, staged, and treated in a similar manner, with a few important notes.

1. Inherited germ line mutations in BRCA1 and BRCA2 genes are a risk factor for fallopian tube cancer. Tubal intraepithelial cancer (TIC) has been detected in the fimbria of BRCA carriers, although its role in progression to invasive cancer has not been proven.
2. Classic symptoms include watery or serosanguinous vaginal discharge, pelvic pain and a pelvic mass. **Hydrops tubae profluens** refers to the intermittent leakage of serosanguinous vaginal discharge followed by shrinkage of the adnexal mass, and is pathognomonic of this disease.

V

NONEPITHELIAL OVARIAN CANCER

This form of ovarian cancer arises from the germ cells and sex cord–stromal cells of the ovary. These rare cancers account for less than 10% of ovarian tumors. Staging is the same as for epithelial ovarian cancer (see Table 40–4). Treatment consists of surgical staging or debulking, occasionally followed by chemotherapy as detailed for each cancer subtype.

A Germ cell tumors Benign germ cell tumors, called mature cystic teratomas, or “dermoids,” account for 25% to 30% of ovarian neoplasms. Malignant germ cell tumors are believed to arise from primitive germ cells in the ovary. These cancers represent 5% of all ovarian malignancies but account for more than two-thirds of all malignant ovarian neoplasms in women younger than 20 years of age. When disease is limited to one ovary, it is appropriate to **leave the uterus and other ovary in place**, as long as a complete staging, including pelvic and para-aortic lymph node dissection, is performed.

1. **Dysgerminomas.** Histologically, the undifferentiated germ cells present as sheets of uniform polyhedral cells. There is a characteristic lymphocytic infiltrate within delicate fibrous septa. Other characteristics of dysgerminomas include the following:

- a. They are the **most common malignant germ cell tumor**, accounting for approximately 40% of this type of tumor.
 - b. Ninety percent of dysgerminomas are found in women younger than 30 years of age.
 - c. The propensity for lymphatic invasion is great.
 - d. Syncytiotrophoblasts in the tumor occasionally secrete detectable amounts of human chorionic gonadotropin (hCG).
 - e. Bilateral tumors occur in more than 20% of cases; 50% of these are macroscopic.
 - f. Tumors are exquisitely sensitive to chemotherapy, and the cure rate approaches 95%.
2. **Immature teratomas.** Histologically, a mixture of differentiated fetal tissue representing three germinal layers is present. Usually the immature element is **neural tissue**. Immature teratomas are further characterized by the following:
- a. They account for 20% of all germ cell tumors.
 - b. Tumors are rarely bilateral, although 10% of patients have a benign dermoid in the contralateral ovary.
 - c. Prognosis is excellent. Adjuvant chemotherapy is recommended for most patients. Patients with low-grade, stage I disease may be followed with surgery alone.
3. **Endodermal sinus tumors (yolk sac) tumors.** The classic histologic finding is the **Schiller-Duval body**, a central vessel lined with columnar cells. Endodermal sinus tumors are further characterized by the following:
- a. They account for 20% of all germ cell tumors.
 - b. The **median age of patients** with endodermal sinus tumors is 19 years.
 - c. Tumors are rarely bilateral.
 - d. Alpha-fetoprotein (AFP) is detectable in the serum of most patients and acts as a tumor marker.
 - e. All patients should receive postoperative chemotherapy.
 - f. In patients with complete surgical excision of tumor prior to chemotherapy, survival is 96%. Survival with incomplete resection is 55%.
4. **Embryonal carcinomas.** The histologic appearance of undifferentiated embryonal tissue consists of solid sheets of anaplastic cells with abundant clear cytoplasm, hyperchromatic nuclei, and numerous mitotic figures. Embryonal carcinoma is further characterized by the following:
- a. This rare cancer occurs in young females; the **median age of patients** with embryonal carcinoma is 15 years.
 - b. Tumors elaborate both AFP and hCG. These trophic hormones may be responsible for precocious puberty in prepubertal girls.
 - c. Most often, tumors are unilateral with explosive growth tendencies, leading to large tumor masses and acute abdominal pain. Tumors are rarely bilateral.
 - d. Surgery and chemotherapy result in cures for approximately one-third of patients.
5. **Nongestational choriocarcinomas.** These primary tumors must be distinguished from metastatic disease to the ovary from gestational choriocarcinomas. The histologic appearance is that of atypical to highly anaplastic cytotrophoblastic and syncytiotrophoblastic elements. These tumors are further characterized by the following:
- a. This rare cancer usually occurs in women of reproductive age.
 - b. Tumors are rarely bilateral.
 - c. hCG is detectable in the serum of most patients and acts as a tumor marker.
 - d. Tumors can present as a pelvic mass and precocious puberty in prepubertal girls.
 - e. Treatment with surgery and chemotherapy results in 80% survival.
6. **Polyembryonal cancer.** This cancer has the histologic appearance of embryoid bodies in various states of development. This tumor is further characterized by the following:
- a. This rare cancer usually occurs in women of early reproductive age.
 - b. Tumors are rarely bilateral.
 - c. hCG and AFP are often detectable in the serum of patients and act as a tumor marker.
7. **Mixed germ cell tumors.** Approximately 10% of germ cell tumors are composed of two or more subtypes of cancer. Treatment and prognosis are based on the most severe element.

- B Sex cord–stromal neoplasms** The sex cord cells are granulosa cells and the male homolog, the Sertoli cells. Stromal cells include theca cells, Leydig cells, and fibroblasts. Tumors arising from these cells often produce estrogens and androgens. Granulosa cells, Sertoli cells, and theca cells are usually estrogenic. Leydig cells and specific steroid cells are usually androgenic.
- Juvenile granulosa cell tumors** that occur in premenarchal women induce abnormal bleeding and breast development. Early-stage disease is curable with surgery, but the prognosis for disease spread beyond the ovary is poor.
 - Adult granulosa cell tumors** have the following characteristics:
 - They are bilateral in less than 5% of cases.
 - Tumors vary in size from microscopic to tumors that fill the abdomen.
 - Tumors are characterized histologically by **Call-Exner bodies** (e.g., rosettes or follicles of granulosa cells, often with a central clearing).
 - Ninety percent of cases present as stage I disease and are usually curable. More advanced stage disease is prone to recurrence, often many years after initial treatment.
 - Sertoli–Leydig cell tumors or arrhenoblastoma** are rare tumors of mesenchymal origin.
 - Their usual endocrine activity is androgenic.
 - Defeminization is the classic feature of the androgen-secreting tumors, including breast and uterine atrophy, which is followed by masculinization, including hirsutism, acne, receding hairline, clitoromegaly, and deepening of the voice. Prognosis is based on the extent of differentiation.
- C Gonadoblastomas** These tumors are composed of **germ cells and stromal cells**. They occur in **dysgenetic ovaries** commonly present in individuals with a Y chromosome or fragment because of a mosaic genotype (46,X/46,XY) or testicular feminization (46,XY with androgen insensitivity). Both ovaries are usually affected, and it is recommended that these individuals undergo prophylactic bilateral oophorectomy. **Dysgerminomas** or occasionally other germ cell malignancies occur in 50% of patients with gonadoblastomas.
- D Metastases to the ovary** Metastases to the ovary account for 6% to 9% of ovarian malignancies. Tumors metastatic to the ovary are often bilateral and more likely to be solid. Metastatic spread to the ovary can be the first presentation of a gastrointestinal (GI) malignancy; 50% to 90% of metastases here begin in the GI tract (Krukenberg tumors). Other common metastatic tumors include breast and uterine.

VI

VAGINAL CANCER

- A Squamous cell carcinomas** These cancers are usually located in the upper half of the vagina. They are the most common histologic type.
- Symptoms**
 - The most common symptom is **vaginal discharge**, which is often bloody.
 - Because of the **elasticity of the posterior vaginal fornix**, tumors may be large before they are symptomatic.
 - Age.** This rare, malignant cancer occurs in women between 35 and 70 years of age.
 - Lymphatic spread.** The upper vagina is drained by the common iliac and hypogastric (internal iliac) nodes, whereas the lower vagina is drained by the regional lymph nodes of the femoral triangle.
 - Staging** (Table 40–5).
 - Treatment.** Treatment is primarily by radiotherapy. Large carcinomas of the vault or vaginal walls are treated initially with external radiation; this shrinks the neoplasm so that local radiation therapy will be more effective. Occasionally, vaginal cancer is amenable to primary surgical excision or to excision with a radical hysterectomy and upper vaginectomy.
 - Five-year survival rates**
 - Stage I:** 80% to 90%
 - Stage II:** 60%

TABLE 40-5 Staging System for Vaginal Cancer

Stage I: Limited to vaginal mucosa
Stage II: Involvement of subvaginal tissue but no extension onto pelvic sidewall
Stage III: Extension onto pelvic sidewall
Stage IV: Extension beyond true pelvis or involvement of mucosa of bladder or rectum

- c. **Stage III:** 40%
- d. **Stage IV:** 0%

B DES-related adenocarcinoma (clear cell carcinoma) DES was used in the 1940s through the early 1970s in high-risk pregnancies (e.g., diabetes, habitual abortion, and threatened abortion) to prevent miscarriage. In all documented cases of genital tract abnormalities, maternal DES use began before the 18th week of pregnancy.

1. **Age**
 - a. The mean age for development of clear cell adenocarcinoma of the vagina is 19 years for patients with a history of DES exposure.
 - b. The risk for development of these carcinomas through the age of 24 years in DES-exposed women has been calculated to be between 0.14 and 1.4 per 1,000.
2. **Characteristics of clear cell carcinoma**
 - a. Approximately 40% of the cancers occur in the cervix, and the other 60% occur primarily in the upper half of the vagina.
 - b. The **incidence of lymph node metastases** is high—about 16% in stage I and 30% or more in stage II.
3. **Treatment**
 - a. If the cancer is confined to the cervix and the upper vagina, radical hysterectomy and upper vaginectomy with pelvic lymphadenectomy and ovarian preservation are recommended.
 - b. Advanced tumors and lesions involving the lower vagina are treated more appropriately by radiation, which should include treatment of the pelvic nodes and parametrial tissues.
4. **Prognosis. Five-year survival rates** are better than those for the squamous tumors of the cervix and upper vagina, probably because of earlier detection.

VII

VULVAR CARCINOMA

- A Epidemiology** Factors associated with vulvar carcinoma include the following:
1. A history of vulvar condylomata or granulomatous venereal disease
 2. A history of vulvar Paget disease
 3. A history of vulvar carcinoma in situ
 4. A history of cervical or vaginal cancer
 5. More than 50% of the patients are between the ages of 60 and 79 years. Fewer than 15% are younger than 40 years of age
- B Etiology** Little is known about causal factors in vulvar carcinoma. Recently, HPV types 16 and 18 have been detected in squamous cancer of the vulva.
- C Symptoms** Recognition of a lesion is often accompanied by a delay in diagnosis because of either self-treatment by the patient or lack of recognition by the treating physician. Vulvar cancer usually presents with:
1. A history of chronic **vulvar irritation** or soreness
 2. A **visible lesion on the labia**, which is often painful or pruritic

- D Histology** Squamous carcinoma comprises 90% of these tumors. Malignant melanoma is the second most common vulvar malignancy, responsible for 5% to 10% of tumors. The remaining consist of basal cell carcinoma and sarcoma. The Bartholin gland may give rise to vulvar adenocarcinoma.
- E Patterns of spread**
1. **Local expansion** involves the contiguous structures of the urethra, vagina, perineum, anus, rectum, and pubic bone.
 2. **Lymphatic spread** follows the lymphatic drainage pattern of the vulva, which includes superficial inguinal nodes, deep femoral groups, and pelvic nodes.
 3. **Hematogenous spread** occurs in the advanced or recurrent cases.
- F Diagnosis** Incisional or excisional biopsy of the suspect lesion under local or general anesthesia confirms the diagnosis.
- G Pretreatment evaluation** Clinical assessment of tumor size (T), nodes (N), and metastases (M) and surgical staging are appropriate (Table 40–6).
- H Treatment** Surgical treatment is individualized.
1. **T1 lesions (tumor 2 cm or smaller in size)**
 - a. Radical local excision of the lesion with a 1-cm margin laterally and a depth down to the inferior fascia is indicated when:
 - (1) Biopsy of the tumor reveals a depth of invasion of less than 1 mm.
 - (2) Tumor is unifocal.
 - (3) Remaining vulva is normal.
 - b. No groin dissection is necessary.
 2. **T2 and early T3 tumors without suspect inguinal nodes**
 - a. Radical vulvectomy may be partial or total, depending on the size and location of the lesion.
 - b. Bilateral inguinal and femoral lymphadenectomy may be warranted. Ipsilateral inguinal and femoral lymphadenectomy may be considered when the lesion is well lateralized.
 3. **Tumors with disease in inguinal nodes** are treated with lymphadenectomy. If there are more than two histologically positive nodes, external beam radiation is administered to the groin and pelvis.
 4. **Advanced disease.** Individualized treatment may include surgery, radiation, and chemotherapy. Pelvic radiotherapy is recommended for patients with involved nodes. Survival is poor.

TABLE 40–6 Clinical Assessment and Staging System for Vulvar Carcinoma**Stage I**

Stage IA: Tumor ≤ 2 cm in size that is confined to vulva or perineum, and with stromal invasion ≤ 1 mm; no nodal metastasis

Stage IB: Tumor > 2 cm in size, or with stromal invasion > 1 mm, that is confined to vulva or perineum, with negative nodes

Stage II: Tumor of any size that spreads to urethra, vagina, or anus with negative nodes

Stage III: Tumor of any size with or without extension to urethra, vagina, or anus with positive inguino-femoral lymph nodes

Stage IIIA: (i) With 1 lymph node metastasis (≥ 5 mm), or
(ii) 1–2 lymph node metastasis(es) (< 5 mm)

Stage IIIB: (i) With 2 or more lymph node metastases (≥ 5 mm), or
(ii) 3 or more lymph node metastases (< 5 mm)

Stage IIIC: With positive nodes with extracapsular spread

Stage IV: Tumor invades other regional (2/3 upper urethral or 2/3 upper vagina) or distant structures

Stage IVA: Tumor invades any of the following (i) upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone, or (ii) fixed or ulcerated inguino-femoral nodes

Stage IVB: Any distant metastasis including pelvic lymph nodes

5. **Sentinel lymph node biopsy.** Sentinel lymph node biopsy is currently being investigated, and is gaining acceptance, as an alternative to inguinofemoral lymph node dissection. This procedure is meant to reduce perioperative morbidity of the full groin dissection, and involves a combination of preoperative lymphoscintigraphy using radiolabeled colloid and injection of the vulvar tumor with isosulfan blue dye, with intraoperative identification of the sentinel lymph node by color and a gamma-detecting probe.



Study Questions for Chapter 40

Directions: Match the statement below with the single best answer.

1. A 56-year-old woman, gravida 0, para 0, presents to her gynecologist complaining of abdominal bloating. For the past several months, she has been gaining weight, though she does not have much appetite. Her clothes are tight, and she feels some pressure on her bladder and urinary urgency. She denies vaginal bleeding or a change in bowel habits. Her colonoscopy was normal last year. On physical examination, she has a large pelvic mass. A CT scan is obtained which confirms a 20 cm complex mass in the pelvis as well as free fluid in the abdomen and nodularity in the omentum. The most likely diagnosis is

- ☐ A Serous ovarian cystadenocarcinoma
- ☐ B Immature teratoma
- ☐ C Colorectal carcinoma
- ☐ D Adenocarcinoma of the cervix
- ☐ E Pancreatic adenocarcinoma

QUESTIONS 2–3

A 35-year-old woman, gravida 0, presents to her gynecologist for a routine yearly visit. Upon questioning, her menses have been very irregular, sometimes only coming once every 3 months, interspersed with periods of intermittent moderate spotting that can last for several weeks. She otherwise feels well and denies other complaints. On physical examination, her weight is 325 lb, and her height is 63 inches. Her abdomen is obese, but soft and nontender. Her cervix appears normal, but there is some old blood in the vaginal vault. Her uterus is normal in size and nontender. No adnexal masses are appreciated.

2. What is the most appropriate next step in the evaluation of her abnormal bleeding?

- ☐ A Pap test
- ☐ B 2-hour glucose tolerance test
- ☐ C Pelvic MRI
- ☐ D Endometrial biopsy
- ☐ E Serum estradiol

3. The patient's Pap test is normal, her pelvic ultrasound shows normal ovaries, a thickened endometrial stripe of 1.0 cm with possible polyp, and the endometrial biopsy shows simple hyperplasia without atypia. What is the most appropriate next step in management?

- ☐ A LEEP biopsy
- ☐ B D&C
- ☐ C Oral medroxyprogesterone acetate
- ☐ D Hysterectomy
- ☐ E Follow-up pap, ultrasound, and endometrial biopsy in 1 year

4. A 42-year-old woman presents to her gynecologist's office with complaints of irregular heavy menses and bleeding after intercourse. She has not had a Pap test in many years, but prior to the birth of her last child 9 years ago, they had all been normal. She does have some right-sided pelvic and flank pain, which sometimes shoots down her leg. Physical examination reveals a 5 cm fungating mass on the cervix with extension into the right parametria, as well as right costovertebral angle tenderness. A biopsy of her cervix shows squamous cell carcinoma. Vital signs are within normal limits, and laboratory values are notable for a hemoglobin of 9.2 g/dL and a creatinine of 1.9 mg/dL. CT scan shows a large cervical mass with extension to the sidewall as well as severe hydronephrosis. The next best step in management is

- ☐ A Blood transfusion
- ☐ B Oral antibiotics
- ☐ C Emergent radical hysterectomy
- ☐ D Ureteral stent placement
- ☐ E Multiagent chemotherapy

5. A 65-year-old woman with a history of stage III ovarian cancer presents to the emergency room. She was treated with hysterectomy and suboptimal debulking and completed adjuvant chemotherapy 3 months ago. She now complains of abdominal pain, nausea, and vomiting. She has been unable to keep food down for the past 2 days. She is lightheaded and has palpitations. She almost fainted yesterday. She denies vaginal bleeding. She has not had a bowel movement in 3 to 4 days. On examination, her pulse is 110, with blood pressure of 90/60. Her abdomen is markedly distended and mildly tender to palpation with increased bowel sounds. The next best step in management is:

- ☐ A Aggressive laxatives
- ☐ B Broad spectrum antibiotics
- ☐ C Paracentesis
- ☐ D IV hydration and nasogastric tube
- ☐ E IV antiemetics and trial of clear liquids

6. A 31-year-old woman, gravida 0, presents to you to discuss her risk of ovarian cancer. She has no chronic medical problems. She had her first sexual intercourse at the age of 15 years, with four sexual partners in her entire life, and normal paps. She and her husband are thinking of starting a family in the next year. She smokes one pack per week (for the last 10 years) and has an occasional drink with her husband. Her family history is remarkable for breast cancer in her mother diagnosed at the age of 36 years and in her maternal grandmother at the age of 42 years, as well as ovarian cancer in her maternal aunt at the age of 47 years. Both her grandmother and aunt are now deceased. What is the most appropriate next step?

- ☐ A Start oral contraceptive pills to decrease her risk of ovarian cancer
- ☐ B Laparoscopic removal of the fallopian tubes and ovaries
- ☐ C Testing the patient for mutations in BRCA1 and BRCA2
- ☐ D Testing the patient's mother for mutations in BRCA1 and BRCA2
- ☐ E Mammography every 6 months

7. A 23-year-old woman, gravida 1, para 0, spontaneous abortion 1, has undergone colposcopy for evaluation of a high-grade lesion found on Pap smear. The squamocolumnar junction was visible in its entirety, and the endocervical curettage showed CIN3. A directed biopsy of the cervix also revealed CIN3. The next best step in management is:

- ☐ A CO₂ laser ablation of the abnormal lesions of the cervix
- ☐ B Cryotherapy of cervix
- ☐ C CKC of cervix
- ☐ D Simple hysterectomy
- ☐ E Radical hysterectomy

8. A 72-year-old woman, G4P4, presents to your office for an annual examination, and you elicit a history of vulvar itching over the past few months. She has had no associated bleeding or any other discomfort. On examination you notice a unifocal, approximately 3 cm wart-like lesion on her right labia that is tender to touch. The next best step in management is

- ☐ A Prescribe a topical steroid ointment to decrease pruritus
- ☐ B Reassure the patient and advise her to schedule a follow-up visit if symptoms persist
- ☐ C Perform a punch biopsy of the lesion
- ☐ D Excise the entire lesion in the office after giving adequate local anesthetic to the area
- ☐ E CO₂ laser ablation



Answers and Explanations

1. **The answer is A.** Unfortunately, this scenario highlights the most common presentation of epithelial ovarian cancer today; the majority of epithelial ovarian cancers are diagnosed at advanced stages, with vague abdominal symptoms often preceding diagnosis for only a short amount of time. Most women are diagnosed between the ages of 40 and 65. The omental nodularities noted on CT help to confirm the likelihood of malignancy, as well as an ovarian primary. The CT is helpful not only in diagnosis but in planning the extent of the optimal surgical procedure. Papillary serous histology is the most common, accounting for more than 75% of all ovarian cancers. In contrast, immature teratomas are a rare form of malignant germ cell tumors, a class of malignancies accounting for only 5% of ovarian cancer, and would be unlikely to present with omental metastases. Further workup could include a CA-125 and possibly a barium enema or colonoscopy to rule out colorectal cancer, especially if there is presence of occult blood in the stool or evidence of intestinal obstruction. Metastases to the ovary from GI primaries account for 6% to 9% of ovarian cancers; tumors metastatic to the ovary, such as pancreatic adenocarcinoma are often bilateral and more likely to be solid. It is unlikely that adenocarcinoma of the cervix would present with an ovarian mass such as this, and would be more likely to present with vaginal or postcoital bleeding.
2. **The answer is D.** An endometrial biopsy is indicated in this case and in any case of irregular bleeding occurring in a woman aged 35 or older. This patient's age, nulliparity, obesity, and history suggestive of chronic anovulation are all risk factors for endometrial hyperplasia and malignancy, and as such she needs to be further evaluated with a sampling of her endometrium. A Pap test is reasonable to perform at her annual examination, but her history does not suggest risk factors for cervical cancer, and as such this is not an essential test to work up irregular bleeding. This patient certainly has risk factors for diabetes mellitus, including a BMI greater than 25 kg/m², and a 2-hour glucose tolerance test may be indicated as a screening test at some point, but would not help with the abnormal bleeding. Since her pelvic examination was normal, an MRI would be unlikely to aid in her diagnosis. While obese women have higher levels of exogenous estrogen due to the conversion of androstenedione to estrone and the aromatization of androgens to estradiol, the serum estradiol test is generally used as an evaluation of ovarian reserve in patients undergoing workup for infertility.
3. **The answer is B.** Simple hyperplasia without atypia is associated with a 1% risk of endometrial cancer; in general, endometrial hyperplasia (simple or complex) with atypia is associated with a tenfold higher risk of cancer than hyperplasia without atypia. It is usually safe to treat patients with such a diagnosis with oral medroxyprogesterone acetate or another cyclic or continuous progestin for 3 to 6 months as in answer C, followed by a repeat sampling of the endometrium. However, when hyperplasia without atypia is diagnosed on an office biopsy, it is prudent to first exclude the presence of atypia or adenocarcinoma with further evaluation of the uterine cavity by a D&C. Particularly when a polyp is present, D&C may be necessary to remove the polyp to decrease irregular bleeding as well as for diagnosis to exclude worse hyperplasia in the polyp itself. Because the patient's Pap test is normal, she does not need a LEEP to further biopsy her cervix. Since the patient is premenopausal and nulliparous, a hysterectomy would not be indicated in this setting, especially if the absence of atypia is confirmed on D&C. If her D&C did show presence of atypia and the patient desired fertility, higher dose progestins, such as megestrol acetate may be used instead. Hysterectomy is the treatment of choice for patients with hyperplasia with atypia who do not desire future fertility or are unable to comply with progestin treatment and close follow-up. To wait 1 year for follow-up, as in answer E, would be too long; follow-up sampling should be repeated as early as 3 to 6 months.
4. **The answer is D.** This patient has advanced cervical cancer, from this evaluation at least stage IIIB. With her history of bleeding, it is not surprising that she is anemic with a hemoglobin of 9.2 g/dL, but her normal vital signs indicate that she is currently hemodynamically stable. More pressing is her creatinine of 1.9 mg/dL along with hydronephrosis on CT; ureteral stents should be placed as she is at high risk for renal failure. If her disease worsens, ureteral stents may be unable to be placed, and percutaneous nephrostomy tubes may become necessary. An emergent radical hysterectomy is not indicated

with her advanced stage cervical cancer. Women with locally advanced cervical cancer (greater than stage IIA) are best treated with primary radiation therapy—a combination of external beam radiation and brachytherapy—along with concomitant chemotherapy. Multiagent chemotherapy has a role in recurrent cervical cancer, but as primary treatment, single-agent cisplatin is used in combination with radiation. Cisplatin has been shown in several studies to have a sensitizing effect on radiation, improving progression-free survival by as much as 30%. There is no evidence of infection in the above scenario, so oral antibiotics are not indicated. Of note, anemia has been associated with worsened overall prognosis and poorer response to radiation due to tissue hypoxia, so the patient would likely benefit from a transfusion prior to beginning treatment with radiation.

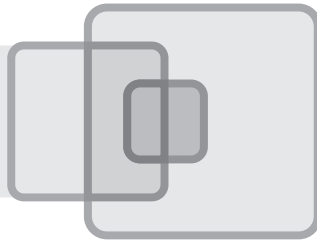
5. The answer is D. This patient has advanced ovarian cancer and has had major abdominal surgery, and is now presenting with the classic sequelae of a partial or complete small bowel obstruction, including nausea, vomiting, absence of flatus or bowel movements, dehydration, tachycardia and hypotension. Postoperative adhesions as well as carcinomatosis (small tumor nodules deposited along the small and large bowel) can lead to extrinsic compression of the bowel lumen and predispose women with advanced ovarian cancer to this scenario. The small intestine proximal to the point of obstruction begins to dilate, bacterial overgrowth can occur, and the small bowel sequesters more fluid as its absorptive functions are lost. Electrolyte abnormalities are common. Distention results, and auscultation of the abdomen may find hypoactive or high-pitched bowel sounds so is not particularly helpful. Tympany usually suggests dilated, air-filled loops of bowel. Aggressive IV fluid hydration in addition to a nasogastric tube to relieve the dilation of the bowel are the mainstay of conservative management of a partial small bowel obstruction. IV antiemetics, as in E, are certainly helpful, but feeding a patient with a bowel obstruction is not advised until flatus or bowel movements resume. Aggressive laxatives are ill advised in this scenario, as they will only serve to irritate the already hypofunctioning bowel. Broad spectrum antibiotics would be required if there were fever or other evidence of peritonitis, such as exquisite tenderness to palpation, which may occur if the bowel obstruction progresses to strangulation, but her clinical picture does not indicate peritonitis at this time. Patients with ovarian cancer can certainly present with markedly distended abdomens from ascites, but as this patient's scenario so classically resembles a small bowel obstruction, an abdominal ultrasound should be performed to confirm the presence of ascites and to aid in accurate needle placement into a pocket of fluid, as opposed to blind paracentesis which may result in placement of a needle into dilated loops of bowel.

6. The answer is D. This patient has a strong family history of early onset breast and ovarian cancers, highly suggestive of an inherited mutation in a susceptibility gene such as BRCA1 or BRCA2. Mutations in these genes account for 5% to 10% of all cases of ovarian cancer and are inherited in an autosomal dominant fashion. If the patient wishes to pursue it, genetic testing would certainly be advisable, but it is always preferable to initiate BRCA testing in relatives who have had early-onset breast or ovarian cancer, as opposed to unaffected at-risk individuals. Therefore, if possible, the patient's mother should be tested prior to testing the patient herself. If her mother tests positive, the patient herself could then pursue testing which more informative results. Oral contraceptives are associated with a decreased risk of ovarian cancer, but in some studies have been associated with an increased risk for breast cancer, and would not be consistent with this patient's desire to start a family. For patients with BRCA mutations, prophylactic mastectomy is often considered, as is salpingo-oophorectomy once childbearing is complete. More frequent mammography is sometimes considered in women with BRCA mutations; however, in a woman younger than 35 years, ultrasound or MRI may be more sensitive. Regardless, the patient should have documented genetic testing completed before beginning more frequent breast screening.

7. The answer is C [I C 1]. For a patient with severe cervical dysplasia, a cone biopsy is both diagnostic and therapeutic. A LEEP could be performed as well, however, when high-grade dysplasia is present in the endocervical canal, cold-knife cone biopsy is preferable for better endocervical sampling. LEEP also leaves a margin of cautery artifact, making it difficult to precisely estimate margins. The presence of a pathologic specimen to ensure adequate margins is essential. CO₂ laser ablation of abnormal lesions is generally reserved for the vagina or vulva, in areas that would be difficult to remove through an excisional process. Cryotherapy is similarly not a good option because it may not completely destroy the preinvasive lesion (therefore no cure) and it does not provide a pathologic specimen for further

evaluation of the lesion. Cryotherapy can be useful in the setting of a lower grade lesion in patients who have a documented negative endocervical curettage. In this patient, a total abdominal hysterectomy and bilateral salpingo-oophorectomy is not the best initial step here because she has no children and is still of childbearing age. It is considered in older women who have persistent severe cervical dysplasia after several excisional procedures. A radical hysterectomy is reserved for patients with cancer and is too radical of a procedure for a preinvasive lesion, and is not without complications.

8. The answer is C [VII C]. Because of the wide spectrum of lesions that can occur here, as well as a tendency for patients and clinicians alike to ignore these symptoms, vulvar lesions can present a challenge to clinicians. In general, the history of pruritus should raise suspicion for malignancy, and any suspicious finding on the vulva should be biopsied to rule this out. Malignant vulvar lesions are often unilocular and described as fleshy, nodular or warty. Although the lesion is small, a biopsy is preferred to an excisional procedure in the office, since if malignancy is diagnosed, the depth of invasion indicates the extent of the surgical procedure necessary. Furthermore, a pathologic diagnosis is required in this situation to rule out malignancy, so CO₂ laser ablation would not be appropriate. CO₂ laser ablation is generally indicated for vulvar or vaginal intraepithelial neoplasias that are multifocal and located in areas difficult to excise.



Intimate Partner Violence and Sexual Assault

JANICE B. ASHER

I

RELATIONSHIP VIOLENCE

A Introduction Relationship violence is the maintenance of power by one intimate partner, usually male, to control another intimate partner, usually female. The **National Center for Injury Prevention and Control (NCIPC) of the Centers for Disease Control and Prevention (CDC)** uses the broad term **intimate partner violence (IPV)** to refer to “actual or threatened physical or sexual violence or psychological and emotional abuse directed to a spouse, ex-spouse, current or former boyfriend or girlfriend, or current or former dating partner.” Same-sex partners are probably at the same risk as heterosexual partners and therefore need to be asked the same directed questions as those in heterosexual relationships.

1. **Frequency.** At the outset, episodes of violence may occur infrequently. Subsequently, they tend to occur more often.
2. **Severity.** Episodes of violence may begin as simple verbal or emotional assaults intended to intimidate and isolate the victim and may then escalate to the intentional infliction of brutal physical injuries.
3. **Role of the physician.** Relationship violence is a major public health concern. Physicians are frequently the only professionals with whom victims of relationship violence come in contact. Physicians have both the opportunity and the responsibility to address domestic violence with all of their female patients.
4. **Public health implications.** Just as inquiry into public health issues such as smoking and alcohol is standard of care for physicians, so is screening adolescent and adult female patients for IPV.
5. **Children: the other victims.** There are as many as ten million children per year who witness IPV. These children are at risk for behavior and school problems, substance abuse, and violent relationships as adults. IPV intervention is a critical tool in preventing child abuse.

B Epidemiology

1. The CDC reports that 1.5 million women are raped or physically abused by an intimate partner each year. Men are also victims of rape or physical abuse, but less frequently (approximately 850,000).
2. Overall, the lifetime incidence of relationship violence toward women is greater than 25%. More women present for medical care because of battering than the total number who present because of stranger rape, automobile accidents, and mugging.
3. Unfortunately, health care providers usually do not identify abused women, and their abuse-related symptoms are unrecognized. This is true even in cases of acute trauma. In one study, only 13% of women presenting to the emergency department for abuse-related injuries were asked about relationship violence.

C Medical evaluation

1. **Assessment.** Appropriate assessment of relationship violence is much more likely to save time and expense. The time needed to evaluate and treat abuse-related symptoms that are initially unrecognized may be considerable. Moreover, violence assessment is, in itself, a powerful intervention. By routinely asking questions about IPV, physicians are sending important messages: that IPV is common, that it is an area of medical concern, and that the victim of violence can discuss the issue with a physician.
2. **Screening**
 - a. **Screening for IPV is standard of care for all adolescent and adult female patients.**
 - b. Physicians should practice routine screening of all their female patients for relationship violence because the vast majority of women in abusive relationships do not spontaneously disclose that they are being abused. The primary reason that women give for not mentioning abuse is fear of retaliation by their partners who learn about the disclosure. Women also cite fear of police involvement and feelings of shame and embarrassment.
 - c. Relationship violence occurs in **all racial, ethnic, religious, and socioeconomic groups**, and screening for those who fit a certain “profile” may exclude identification of some victims. Screening is particularly recommended at annual examinations, preconception and family planning visits, and during pregnancy.
 - d. **It is better to inquire about specific behaviors than to use general terms, because the term “abuse” means different things to different people. Recommended screening questions include:**
 - (1) Are you in a relationship in which you have been hit or physically threatened?
 - (2) Are you in a relationship in which you have been forced to have sex?
 - (3) Are you afraid of a current or ex-partner?
3. **Clinical picture.** More than 50% of abused women present with such somatic complaints as headache, abdominal pain, pelvic pain, fatigue, shortness of breath, gastrointestinal disturbances, sleep disorders, and other chronic conditions in addition to their physical injuries.

D Physician response

1. After obtaining the victim’s history regarding the nature and severity of the abuse, it is important to communicate concern for the patient’s safety in a nonjudgmental and compassionate way.
2. An understandable but **dangerous reaction by the physician** is to urge a patient to leave a violent relationship immediately. Abundant data indicate that abused women are most likely to be seriously injured or killed by their partners when they attempt to leave them. It is dangerous for victims to attempt to leave a relationship before they have **formulated well-developed safety and exit plan**.
3. A physician should focus on concern for the safety of the patient and her children. Safety planning cards are available from local agencies such as women’s advocacy groups.

E Documentation It is necessary to document patient statements regarding abuse and physical findings associated with battering as part of ensuring patient safety. Such documentation may eventually be useful in a court of law, particularly if custody issues arise. To protect the patient’s confidentiality with regard to the abusive partner, documentation of abuse should not appear on the billing diagnosis if the patient’s partner will receive insurance information.

1. **Document the abuse in the patient’s own words.** For example, “Patient states, ‘My husband, John Smith, hit me with his fists,’” is preferable to “history of trauma.” Documentation should include the name of the perpetrator and nature of the weapon used. For description of injuries, dated photographs are ideal, but body maps or written descriptions are also acceptable.
2. Whenever possible, **document whether injuries appear recent or old.**

F Follow-up **The physician should offer a follow-up visit for the patient.** Once a victim is identified, it is important that a physician offer referral to a relationship violence expert, who may be a hospital-based or community-based social worker, a colleague who is knowledgeable about relationship violence, a local domestic violence advocacy organization, or the **National Domestic Violence Hotline** (1-800-799-SAFE).

II

VIOLENCE IN PREGNANCY

A Introduction Violence in pregnancy presents a unique challenge in that there are two victims: mother and fetus. Pregnancy offers physicians a tremendous opportunity for screening and intervention because of the

1. Increased availability of medical attention
2. Desire of pregnant women to ensure a healthy outcome for their infants

B Epidemiology

1. The leading cause of maternal mortality in pregnancy is homicide, and the most likely perpetrator is the woman's partner. More pregnant women die because of relationship violence than of any medical complication of pregnancy. The estimated incidence of relationship violence in pregnancy is 4 to 20%.
2. **Adolescents are overrepresented** among abused pregnant women. As many as 29% of pregnant adolescents experience abuse, including sexual abuse and assault.
3. The single **greatest risk factor** for relationship violence during pregnancy is a **history of violence within the year prior to the pregnancy**. In violent relationships, unintended pregnancy may in itself represent a manifestation of abuse; abused women may not be able to affect sexual activity or contraceptive use. Similarly, because abused women cannot necessarily practice "safe" sex, they are also at increased risk for sexually transmitted infections (STDs) during pregnancy.
4. Several studies have concluded that **violence during the postpartum period is even more common** than during pregnancy. In one study, 90% of women who were battered during pregnancy were abused by their partners within 3 months of delivery.

C Obstetric complications associated with violence Pregnant women in abusive relationships may have limited access to medical care, medications, or even food. Several studies have found that abused pregnant women entered prenatal care significantly later than nonabused pregnant women; restricted access to medical care may explain this result.

1. An increased incidence of premature delivery, low birth weight, abdominal and vulvar trauma, cesarean section, and pyelonephritis may occur in women who suffer violence during pregnancy.
2. Abdominal trauma may cause injury to the mother but may also result in serious harm to the fetus, including fetal fractures, dermal scars, and even death.

III

SEXUAL ASSAULT

A Introduction

1. Sexual assault is a form of sexual activity that occurs without the consent of the victim and includes the use of force, implied force, or deception on the part of the assailant.
2. Physicians play a crucial role in the 48 hours after an assault occurs; they must collect and document evidence properly for use by the police and the courts. Because only a small percentage of women receive emergency medical care or file a police report immediately after an assault, physicians must screen patients for a history of sexual assault to manage symptoms appropriately and to help patients receive aid for potentially devastating emotional sequelae.
3. **Rape** may be **broadly defined** as a form of sexual assault in which a bodily orifice is penetrated without consent by a genital organ or object wielded by another person. However, rape may be defined in different ways in various states and countries. For example, some jurisdictions include male rape whereas others (including the FBI) do not.

B Epidemiology Sexual assault is the fastest growing crime in the United States. Of the approximately 1 million sexual assaults that occur each year, two-thirds of incidents are not reported to the police, and two-thirds of these acts are committed by a perpetrator known to the victim. Approximately 25% of females have been victims of sexual assault prior to 18 years of age.

C Forensic evaluation The physical examination has two purposes: **to evaluate injuries and to collect evidence.**

1. Only trained health care professionals should undertake evidence collection after sexual assault. Improperly collected and poorly handled evidence may negatively affect a victim's criminal case.
 - a. If evidence is collected at the clinic site, it is of utmost importance that a chain of custody be established. All evidence must be collected securely, labeled, and sealed, and the physician responsible must know the location of the collected evidence or "rape kit" at all times.
 - (1) If an appropriately trained clinician is unavailable, or in the absence of an emergency department protocol, referrals to an established sexual assault center, which are designated in most large cities, should be made.
2. Photographs of external gynecologic injuries should be taken using a 35-mm camera, if possible. Smaller, less obvious contusions, abrasions, and tears are better captured through colposcopic imaging.

D Documentation Medical documentation is an important forensic component in the management of a victim of a violent crime. Because medical documents are considered legal documents, the degree to which the physician accurately describes the care rendered may greatly affect a victim's legal case. The likelihood of rape charges and a resulting conviction are directly related to documentation of injuries.

E STD evaluation and prophylaxis The estimated incidence of STDs resulting from rape is 3.6% to 30%.

1. Specimens from appropriate sites should be obtained to check for **gonorrhea** (*Neisseria gonorrhoeae*) and **chlamydia** (*Chlamydia trachomatis*). The patient should be offered presumptive treatment for chlamydia and gonorrhea.
2. Visible vesicles or ulcers may be cultured for **herpes**.
3. A wet mount of vaginal secretions can be examined for **trichomonas** (as well as for sperm). The absence of sperm does not mean that rape has not occurred. The act of rape is one of forced sexual contact, not necessarily ejaculation.
4. The patient needs to be advised that seroconversion for **syphilis** and **hepatitis B** takes 6 weeks. All patients who have not received the hepatitis B vaccine should be offered vaccination. **HIV** testing may also be performed at 6 weeks but should be repeated at 3 and 6 months. HIV prophylaxis should be discussed with the patient.

F Pregnancy evaluation and prophylaxis

1. All female rape victims should undergo baseline pregnancy testing and be offered emergency contraception (often referred to as "the morning-after pill"). Emergency contraception greatly reduces the risk of pregnancy when used within 72 hours after intercourse. It may have some effectiveness as long as 5 days after intercourse. Progesterone-only emergency contraception is more efficacious and has fewer side effects than estrogen-progesterone preparations.
2. The only absolute contraindication to emergency contraception is current pregnancy. Physicians may safely offer emergency contraception to women who would not ordinarily be considered good candidates for oral contraception because of concurrent medical problems. Most of the approximately 22,000 pregnancies per year in the United States that result from rape could be prevented if all women who had been raped received emergency contraception within 72 hours of the assault.

G Follow-up

1. In addition to collaborating with the local police, physicians should also offer to refer victims of rape to local victim advocacy agencies, including domestic violence and rape advocacy resources. When available and appropriate, victims' advocates should be present during the initial assault history and during the evidence collection procedure. The additional support offered by these specially trained advocates assists victims during the initial aftermath of the assault and during the longer recovery period.

2. **Psychological sequelae of rape** may be evident for many years after the assault. These sequelae include some or all of the features of **posttraumatic stress disorder**, which is chiefly characterized by four symptoms:
 - a. Involuntary reexperiencing of the traumatic event through thoughts, nightmares, or flashbacks
 - b. Avoidance of activities, including those that were previously pleasurable
 - c. Avoidance of circumstances in which the rape occurred
 - d. A state of increased psychomotor arousal, which may be associated with sleep disturbances and panic attacks

IV

ACQUAINTANCE RAPE AND DATING VIOLENCE

A Introduction Adolescents and young adults are more likely to be victims of sexual assault than women in all other age groups. The prevalence of date rape ranges from 13% to 27% among college women and 20% to 68% among the general adolescent population. In one study, 41% of the women who had been raped stated that they were virgins at the time of the assault.

B Epidemiology Rape statistics are difficult to obtain because of overall underreporting of sexual assault; it is not surprising that data about the incidence of acquaintance rape is limited.

1. Association with drugs and alcohol

- a. As many as 73% of assailants and 55% of victims have used alcohol or drugs immediately before the episode of sexual assault. Alcohol is a disinhibitor, but in itself, it does not cause violence.
- b. Drugs besides alcohol are rapidly gaining prominence in sexual assaults. These include flunitrazepam (Rohypnol), a fast-acting benzodiazepine; ketamine; and gamma-hydroxybutyrate and its congeners.
 - (1) These drugs are added to the intended victim's drink without her knowledge or consent. In addition to causing disinhibition, one of the effects of such drugs is anterograde amnesia, which makes it difficult to obtain a history of the event.
 - (2) Use of these drugs, which may cause symptoms similar to those of alcohol, should be suspected. Certain protocols exist in many emergency departments for urine or blood sample collection to test for the presence of such drugs. In the absence of protocols, the drug manufacturers can be contacted.

2. Social and cultural factors.

Many cultural stereotypes and values support the notion that date rape simply does not exist or that, if it does, it is justifiable under a variety of circumstances.

- a. The perpetrator (and for that matter the victim) may have grown up in a family, peer group, or culture in which sexual aggression is part of the definition of manhood. Most perpetrators do not consider forceful or coercive sex in the context of a date to be rape.
- b. Many men, as well as women, believe that women are "supposed" to refuse sex and that men are "supposed" to pressure, coerce, or even force them.
- c. Whereas female victims tend to be blamed if they have used alcohol ("it was her own fault") and may even blame themselves, male perpetrators are more likely to be excused ("he would never do that when he's sober").

C Medical evaluation

1. As with other types of rape, the approach to acquaintance rape should include identification and treatment of injuries; prevention of STDs and pregnancy; psychological assessment with appropriate referral for counseling; and, if the patient consents, collection of forensic evidence if the assault has occurred within 72 hours.
2. It is important for the physician to ascertain the victim's level of safety. As in other types of assault in which the victim knows the perpetrator, there may be a high risk of retaliation against the victim for seeking medical care. It is mandatory to review a safety plan with the victim prior to discharge.

- D Physician response** The importance of psychological support cannot be overemphasized. The victim is likely to feel traumatized and even ashamed.
1. A compassionate, nonjudgmental response is crucial in helping the victim of rape begin the process of psychological healing.
 2. It is crucial to help the patient understand that while she needs to know how to ensure her personal safety as much as possible, she is in no way to blame for a sexual assault. That responsibility rests solely with the perpetrator.
 3. It is important to stress to a patient that she can minimize the risk of being the victim of acquaintance rape by not drinking excessive alcohol or by not going to a secluded place with a date. That is by no means the same as saying that if she does not practice these risk-reduction behaviors, she is to blame for a rape. The responsibility for a crime always rests with the perpetrator.
- E Prevention** The possibility of dating violence, particularly in the context of drugs and alcohol, should be included in routine visits with adolescent patients. This discussion should also include information about STDs, emergency contraception, and long-term contraception. According to the Council on Child and Adolescent Health, such preventive counseling is particularly important at the precollege visit.



Study Questions for Chapter 41

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A 22-year-old, G1P0, presents at 12 weeks for routine prenatal care. When asked if she's in a relationship in which she's been hurt or threatened, she confides that prior to the pregnancy, she and her husband had arguments that "sometimes got physical," which resulted in injury to her. Now that she's pregnant, however, he treats her wonderfully, she tells you. What is the best response to this information?

- ☐ A "I am concerned for the safety of you and your baby"
- ☐ B "He is likely to hurt you again, and you should leave the relationship now"
- ☐ C "You should get a Protection from Abuse order"
- ☐ D "As a mandated reporter, I need to report the abuse to the National Center for Injury Prevention and Control"
- ☐ E "You need to be careful not to anger your husband"

2. You are in the Emergency Department seeing a 22-year-old victim who states she was raped 2 hours ago. Her medical history is negative except for migraine with aura. Her last menstrual period was 2 weeks ago. Which statement is correct?

- ☐ A You offer her emergency contraception because there is no contraindication except for current pregnancy
- ☐ B You do not give her emergency contraception because migraine with aura is a contraindication to birth control pills
- ☐ C You recommend that she follows up with her own physician to discuss emergency contraception
- ☐ D You find out what other medications she is taking before considering prescribing emergency contraception
- ☐ E You do not give her emergency contraception because it is too late in the menstrual cycle to be effective

3. You suspect violent injury to a patient who says she "walked into a door." What is the most likely reason that does not disclose intimate partner violence?

- ☐ A She has masochistic tendencies
- ☐ B She does not want to talk about the problem
- ☐ C She is worried about further violence if her partner finds out she told someone
- ☐ D It is not a medical issue
- ☐ E Her partner has assured her that he will never hit her again

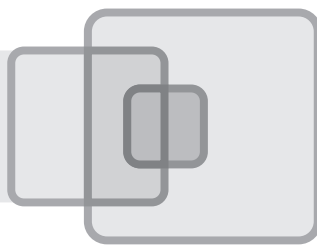
4. Which of the following statements is true?

- ☐ A Because of violence, abused women are more likely to seek prenatal care earlier in pregnancy
- ☐ B Physicians cannot screen for IPV in adolescents without parental permission
- ☐ C Children who witness violence are likely to turn away from violence as adults
- ☐ D The leading cause of maternal mortality is homicide
- ☐ E A woman cannot accuse a man of rape if she was too intoxicated to say no



Answers and Explanations

1. **The answer is A.** When a patient discloses that she is in a violent relationship, the physician's concern should always be safety. Leaving a violent relationship without a well thought-out safety plan may be very dangerous. The patient clearly is not ready to seek a protection from abuse order. In most states, there is not mandated reporting of abuse for competent adults. The physician should avoid a response that is victim-blaming.
2. **The answer is A.** The only contraindication for emergency contraception is current pregnancy. While migraine with aura is a contraindication to the use of birth control pills, there are no contraindications except for current pregnancy to the use of emergency contraception. The sooner emergency contraception is used, the more effective it is. It does not matter where the patient is in her menstrual cycle for emergency contraception to be effective. Again, there are no medical contraindications to the use of emergency contraception.
3. **The answer is C.** A victim of violence may justifiably fear retaliation by the abuser if the victim discloses the violence. Most victims of violence abhor the violence, even if they do not want to leave the relationship, and masochistic tendencies are not part of the syndrome. Victims are more likely to disclose violence to their physicians than to anyone else—but only if they are asked. IPV is an important public health issue. Despite assurances, violence is usually repetitive and, in fact, often increases over time. Assurances from an abusive partner that the violence will stop are not reassuring and often untrue.
4. **The answer is D.** Pregnant women who experience violence are more likely to seek prenatal care later in pregnancy. No parental permission is necessary to screen for violence in an adolescent or young female. Children who witness violence are more likely to be perpetrators or victims of violence as adults not less likely. If a woman is too intoxicated to give consent to sex, then there is sexual assault.



Medicolegal Considerations in Obstetrics and Gynecology

ALEX FRIEDMAN • HARISH M. SEHDEV

I

INTRODUCTION

Law defines modes of behavior among the members of a society and the groups within a society, such that conflicting interests may be resolved in a civilized fashion. Medicine is one such group. In medicine, the law permeates, defines, and regulates the relationship between the physician and patient, the physician and hospital, and the physician and society. Moreover, legal issues dealing with access to medical care and consumer demands regarding health care are dominant in public policy discussions. Obstetrics and gynecology is at the cutting edge of these matters because the field involves the most critical aspects of life: conception, reproduction, and pregnancy. Thus, it is important for the student of medicine to understand, in a preliminary fashion, the legal issues that involve the practice of obstetrics and gynecology.

II

MALPRACTICE

A Definition Malpractice is **professional misconduct** whereby a physician departs from the standards of care through a lack of skill, a lack of knowledge, or a lack of judgment in carrying out professional duties.

B Elements of negligence A plaintiff must prove four elements of a case to be successful in a claim for medical negligence

1. **Duty.** A physician has a particular duty or obligation to the patient. A **physician–patient relationship** exists when a patient comes to a physician, who agrees to undertake her care. It is a form of **implied contract**. In this relationship, a physician must act:
 - a. In accordance with standards established or accepted by a reasonable fraction of the profession practicing in a given area
 - b. As a reasonable physician, taking reasonable care of a patient and not taking unreasonable risks
2. **Breach of duty.** A physician who fails to act in accordance with professional norms has departed from the standard of care and has committed a breach of the duty owed to the patient. This breach must be substantiated by the testimony of an expert.
3. **Causation.** The breach of duty owed must be the proximate cause of a patient's injury for a malpractice action to exist.
4. **Damages.** Actual loss, injury, or damage must have occurred, although pain and suffering is a common accompaniment.

C Recovery The patient or plaintiff must prove that it is more probable than not that the elements of negligence are satisfied (**preponderance of evidence**) to recover compensation for the damage incurred.

III

PRECONCEPTION ISSUES

A constitutional right of privacy protects an individual's procreative choice from government intrusion. The **right to use contraception** was the earliest right to reproductive freedom (*Griswold v Connecticut*, 1965).

A Hormonal contraceptives

1. Most lawsuits regarding hormonal contraceptives are **product liability** cases against the manufacturer.
 - a. The general rule is that a manufacturer must provide patients with a written warning of all untoward side effects.
 - b. A physician must inform patients of the possible side effects and explain the alternative methods of contraception. All of these discussions must be documented.
2. A physician has a duty to:
 - a. Perform a thorough physical examination
 - b. Perform relevant laboratory examinations
 - c. Warn patients of possible adverse side effects
 - d. Closely monitor patients in whom side effects develop

B Intrauterine devices (IUDs) have been in the past the center of legal and medical controversy since the Dalkon Shield was recalled in 1974.

1. All IUDs, except for the Mirena (hormone-containing device) and the ParaGard (a copper-containing device), have been withdrawn by the manufacturers because of litigation costs. Most lawsuits have been product liability cases, with claims that the IUD has caused:
 - a. Uterine and pelvic infections
 - b. Infertility
 - c. Uterine perforation
 - d. Ectopic pregnancy
2. A physician has a duty to:
 - a. Inform patients of the risks involved with IUD insertion and use
 - b. Explain alternative methods of contraception and their risks
 - c. Perform a physical examination
 - d. Perform a Papanicolaou (Pap) test and cervical cultures
 - e. Examine patients in 3 months after insertion of an IUD and yearly thereafter
3. Since reintroduction of the copper-containing IUD (ParaGard) in 1988 with its recommendations on patient selection and informed consent, there has been no successful litigation.

C Sterilization This surgical procedure is undertaken for the express purpose of eliminating reproductive capacity.

1. **Voluntary sterilization:** A physician has a duty to:
 - a. Carry out the operation in accordance with accepted medical practice
 - b. Inform the patient that the operation will result in sterility
 - c. Inform the patient that the procedure should be looked upon as permanent
 - d. Offer alternative forms of contraception
 - e. Counsel the patient that there is no guarantee of sterility; pregnancy occurs at a rate of 15 to 20 per 1,000 cases over 10 years, with ectopic pregnancy more frequent when pregnancy does occur
 - f. Inform the patient that the procedure does not protect against sexually transmitted diseases including human immunodeficiency virus

IV**GENETIC COUNSELING**

Five percent of all newborns are born with a congenital disorder.

A Consent and counseling for a prenatal genetic testing should include documentation of

1. Patient understanding of essential information about test
2. The risks of having an infant who has the disease in question
3. The cost of the testing
4. Potential therapies if condition is diagnosed
5. Reproductive options

6. Likely disease course of diagnosed condition
7. Risks of test procedures
8. Limitations of test procedures
9. Length of time required to complete testing

B An obstetrical provider is obligated to

1. Obtain detailed patient, family, and ethnic/racial histories to determine which prospective parents are at increased risk.
2. The obstetrical provider does not have to obtain the information herself; she may refer the patient to a medical geneticist or genetic counselor for evaluation.

C Routine genetic screening

1. Legislation requires **phenylketonuria** and **hypothyroid** testing in newborns.
2. Testing for **cystic fibrosis** should be discussed and offered at the preconceptional and/or prenatal visit.
3. There are centers for voluntary **screening of sickle cell disease, homocystinuria, galactosemia, Tay–Sachs, and maple syrup urine disease.**
4. Prenatal **multiple marker** testing to determine the risk of neural tube defects and Down syndrome should be offered to all women, including those younger than 35 years of age.

- D** Couples may consider genetic counseling before conception to determine if they have an increased risk of having a child with a birth defect, syndrome, or other inherited genetic conditions. Counseling is recommended when there is a family history of birth defects, mental retardation, or genetic disorders, such as muscular dystrophy, cystic fibrosis, or hemophilia.

E Particular problems of which a physician must be aware include the following:

1. **Teratogens**
 - a. Anti-epileptic medications
 - b. Antibiotics
 - (1) Tetracyclins
 - (2) Fluoroquinolones
 - c. ACE inhibitors and similar drugs (angiotensin receptor blockers)
 - d. Warfarin
 - e. Alcohol
 - f. Chemotherapeutic agents
 - g. Lithium
2. **Autosomal dominant disorders**
 - a. Neurofibromatosis
 - b. Hereditary familial polyposis
 - c. Huntington's disease
3. **Autosomal recessive disorders**
 - a. Cystic fibrosis
 - b. Spinal muscle atrophy
 - c. Infantile polycystic kidney disease
 - d. Congenital deafness
 - e. Tay–Sachs disease
 - f. Canavan's disease, Gaucher's, and Fanconi's anemia
4. **X-linked disorders**
 - a. Fragile X syndrome
 - b. Duchenne muscular dystrophy
 - c. Hemophilia
5. **Congenital infections**
 - a. Rubella
 - b. Cytomegalovirus (CMV)

- c. Toxoplasma
 - d. Parvovirus
 - e. Syphilis
6. **Hemoglobinopathies**
- a. Thalassemia
 - b. Sickle cell disease

- F** **Referral to a genetic counselor** is appropriate for pregnant women if there is:
1. A genetic or congenital abnormality in a family member
 2. A family history of a genetic problem
 3. Abnormal development in a previous child
 4. Mental retardation in a previous child (or family history of mental retardation)
 5. Maternal age 35 years or older
 6. Specific ethnic background suggestive of a genetic abnormality (e.g., Tay–Sachs disease in Ashkenazi Jews, among others)
 7. Exposure to drugs or teratogens
 8. A history of two or more spontaneous abortions
- G** **Amniocentesis** or chorionic villus sampling (CVS) must be offered to pregnant women if there is:
1. Maternal age 35 years or older (although women of any age may accept)
 2. A concern for a genetic abnormality based on ultrasound findings
 3. A family history of genetic disease
 4. An abnormal multiple marker screen
- H** **Amniocentesis and CVS malpractice liability may arise from the following recognized complications of the procedures if informed consent is not performed or if there is negligence**
1. Maternal infection
 2. Fetal loss or injury
 3. Development of anti-D antibodies in an Rh-negative woman not administered Rh immune globulin
 4. Special counseling should take place in the setting of maternal infection with:
 - a. HIV
 - b. Hepatitis C virus
 - c. Hepatitis B virus

V

TERMINATION OF PREGNANCY

- A** **Right of privacy** A woman's right to abortion falls within a right of privacy interpreted by the U.S. Supreme Court to exist within the Constitution. This right was upheld in *Roe v Wade* (1973).
- B** **Trimester model**
1. **During the first trimester**, the decision to abort is a decision that is strictly between a woman and her physician.
 2. **During the second trimester**, the state may impose regulations reasonably related to a woman's health.
 3. **After the second trimester or after the fetus is viable**, the state may regulate abortion, except when necessary to preserve a woman's health.
- C** **State restrictions** Since *Roe v Wade* in 1973, the time of the abortion decision, states have formulated many laws to limit a woman's access to abortion. For example, in *Planned Parenthood v Casey* (1992), the U.S. Supreme Court upheld a **Pennsylvania** statute.

1. **Restrictions on elective abortion imposed by the Pennsylvania statute, which was upheld**
 - a. Physicians are required to discuss the nature, risks, and alternatives to abortion, as well as the gestational age of the fetus.
 - b. A 24-hour waiting period is required between the time this information is given and the time the abortion is performed.
 - c. Either parental consent or, alternatively, judicial bypass if parental consent is denied, is required for a minor.
2. The Supreme Court struck down the provision of the statute that required spousal notification.

VI

REPRODUCTIVE TECHNOLOGIES

Techniques in reproductive medicine have created a change in society's concept of the family. Examples include artificial insemination by husband or donor; in vitro fertilization and embryo transfer (IVF-ET); and other assisted reproductive techniques, including gamete or zygote intrafallopian transfer, intracytoplasmic spermatozoa injection (ICSI), donor oocytes, donor embryos, and embryo freezing. A child may be born with as many as five parents: a genetic father, a social father, a genetic mother, a gestational mother, and a social mother. These technologies create legal issues of inheritance, legitimacy, adultery, confidentiality, the status of residual embryos, "parental" responsibilities for a child's diseases and defects, and the legal status and rights of each "parent."

A Artificial insemination

1. **Definition.** Placement of a husband's semen (artificial insemination by husband [AIH]) or a donor's semen (donor insemination [DI]) into the female genital tract is called artificial insemination.
2. **Consent of the husband.** When the husband of a child's mother consents to DI, the husband assumes the same legal right and obligations as a natural parent, including:
 - a. The duty to support the child
 - b. The right to visitation in case of divorce
3. **Right to privacy.** Given the U.S. Supreme Court's recognition of a right to privacy, when a single woman requests DI, a public institution providing these services cannot abridge this woman's right to privacy and, thus, would logically have to provide this service; however, a private practitioner could choose not to provide this service.
4. **A physician has a duty to explain** that there is:
 - a. No guarantee of pregnancy
 - b. A possibility of birth defects that may be attributable to unknown recessive genes of the donor
 - c. Little chance of sexually transmitted disease (STD) transmission because of screening and the quarantined freeze preservation of semen
5. **Liability** may arise when:
 - a. A physician has not adequately screened a donor for genetic defects or STDs, including HIV
 - b. A husband's consent has not been obtained

B In vitro fertilization

1. **Definition.** In IVF, sperm and ova are obtained and incubated outside the body, and the resultant conceptus is implanted into a uterus.
2. **Legal concepts**
 - a. When a husband provides sperm and a wife provides an ovum, traditional family principles apply. This is similar to AIH.
 - b. When a donor provides sperm and a wife provides an ovum, legal concepts of DI and adoption apply.
 - c. When the ovum comes from a female donor and is fertilized and then transferred into another woman's uterus, the legal relationships that arise are complex and not clearly formulated. The essential question is whether genetic material, a contractual relationship, or carrying and giving birth determine the claim of motherhood.

C Gestational carrier

1. **Definition.** When a female partner is incapable of carrying a pregnancy, a couple enters into a contract with another woman (a gestational carrier), who agrees to receive an embryo fertilized with the partner's spermatozoa, and to relinquish her rights to the child. In exchange, she receives payment for medical care, lost wages, and hospitalization. A gestational carrier is typically considered in situations where women have serious medical conditions that preclude pregnancy, do not have a uterus, or have a poor obstetrical history.
2. **Problems arising with the gestational carrier**
 - a. Gestational carrier develops maternal feelings toward the infant and refuses to give the child/children up.
 - b. Gestational carrier decides not to honor the contract and terminate the pregnancy.
 - c. Gestational mother exposes the fetus to teratogens or addicting drugs.
 - d. The infant is defective, and the contractive couple decides not to accept it.
 - e. There is a multiple gestation.
3. **Issues to be addressed in an agreement between carrier and intended parents**
 - a. Financial remuneration
 - b. When is obligation fulfilled? The postpartum period? Breastfeeding may be included
 - c. Role of gestational carrier if untimely death of intended parents

D Embryo freezing

1. **Definition.** Embryo freezing entails preservation by cryopreservation of unused fertilized ova for future implantation.
2. **Problems**
 - a. Concerns have been raised as to the propriety of eugenic considerations and commercialism.
 - b. The destruction of unused embryos has been deemed unethical by some critics.
 - c. If the parents die, the rights and obligations of frozen embryos have yet to be decided.
 - d. If the embryos are donated, then the donated embryo may carry genetic disorders of the biologic parents of which the adoptive parents are unaware.

VII**BIRTH-RELATED SUITS****A Wrongful conception**

1. **Definition.** Conception is deemed wrongful if it arises after:
 - a. Failed sterilization
 - b. Ineffective prescription of contraception
 - c. Failure to diagnose pregnancy in a timely fashion
 - d. Unsuccessful abortion
2. **Liability** arises secondary to a physician's negligence, resulting in the birth of an unplanned child. Negligence is based on:
 - a. Improper performance of a sterilization procedure or an abortion
 - b. Failure to ascertain the success of the procedure
 - c. Failure to inform the woman about the possibility of procedural failures

B Wrongful birth and wrongful life

1. These lawsuits arise out of the birth of an impaired child who otherwise would have been aborted if the parents knew of the impairment ahead of time; the physician did not cause the impairment, but instead failed to make the diagnosis.
2. **Wrongful birth** is an action brought by parents of a child, alleging that a child with a congenital defect was born because of negligent genetic counseling or screening. Thus, a physician has failed to:
 - a. Recognize a genetic problem
 - b. Recognize a fetal abnormality

- c. Recognize a condition that places a fetus at risk for a genetic problem
 - d. Inform the mother of the ability to detect genetic problems and to offer termination
3. **Wrongful life** is an action similar to wrongful birth. However, the **child brings suit against the physician**, alleging that no life at all would have been preferable to life with a congenital defect.

VIII BIRTH INJURY

- A Definition** A birth injury results when an obstetrician's neglect results in injury to a child (e.g., birth trauma, brain damage, or neurologic damage).
- B Alleged negligence** may arise from a failure to:
 1. Monitor fetal heart rate adequately
 2. Assess the degree of risk of a pregnancy
 3. Perform expedient delivery to avoid perinatal asphyxia that leads to brain damage
 4. Monitor a pregnancy adequately
 5. Use obstetric forceps or vacuum extraction properly
 6. Recognize possible macrosomia and the potential for shoulder dystocia and resulting Erb's palsy
- C Brain damage** Current studies indicate that it is impossible to isolate a single cause of brain dysfunction. The National Institutes of Health has stated that:
 1. **Mental retardation is multifactorial**, resulting from a combination of genetic, biochemical, viral, and developmental factors, and is not necessarily related to birth trauma.
 2. **Severe mental retardation and epilepsy** are possibly associated with birth asphyxia but only when accompanied by cerebral palsy, which is associated with prematurity, intrauterine growth retardation, and birth asphyxia.

IX INFORMED CONSENT

- A General definition** "Every human being of adult years and sound mind has a right to determine what shall be done with his/her own body" (*Schloendorff v Society of New York Hospital*, 1914).
- B Negligence theory of consent** To sue successfully under this theory, the patient or plaintiff must show that:
 1. A physician was under a duty to disclose an adequate amount of material information.
 2. A physician disclosed an inadequate amount of material information.
 3. The patient agreed to therapy based on this inadequate information.
 4. The patient was harmed.
 5. If the significant information had been given, the suggested therapy would have been refused.
- C Disclosure rules** establish the appropriate standard of care in obtaining informed consent. States differ as to which standard is applicable.
 1. **Majority rule.** A physician needs to disclose only information that a reasonable physician would disclose and need not disclose information that would not customarily be disclosed. This rule operates from the physician's point of view.
 2. **Minority rule.** A physician needs to disclose only information that a reasonable patient in similar circumstances would wish to know to make a reasonable decision.
- D General guidelines in obtaining informed consent**
 1. A physician must obtain a patient's informed consent before treating her.
 2. A physician must provide information concerning the probable benefits, risks, and nature of the suggested diagnostic or therapeutic interventions.

3. A physician must provide an explanation of reasonable alternatives to the recommended intervention and the consequences of no intervention.
4. Information must be:
 - a. What a reasonable practitioner would reveal under similar circumstances
 - b. What a reasonable patient would consider significant under similar circumstances

E Exceptions to informed consent include the following:

1. If a risk is not reasonably foreseeable, it need not be disclosed.
2. Disclosure may be partial if full disclosure would be detrimental to a patient's best interest.
3. If the danger is commonly known, it can be assumed that the patient knows of the danger.
4. The patient may request not to be told of risks.
5. If the risk concerns improperly performing an appropriate procedure, it need not be disclosed.
6. In an emergency, where delay would result in death or serious injury and where a patient is unable to reflect and give an informed decision, informed consent is not required.
7. If a patient is declared either generally or specifically incompetent, informed consent cannot legitimately be obtained.

F Procedure for obtaining informed consent Informed consent is a process by which a physician imparts information to a patient who, by virtue of this information, may intelligently decide whether to submit to and participate in the physician's proposed intervention. Thus, the physician must do the following:

1. Discuss the need for the intervention.
2. Discuss the intervention honestly and explain it in layman's terms along with the reason for its necessity.
3. Explain the risks inherent in the procedure.
4. Explain alternatives and the probable result of no intervention.
5. Allow the patient to ask questions.
6. Document the conversation, listing the major risks and alternatives presented.
7. Explain that it is the patient's right to know a reasonable amount about the proposed intervention and that this right is being forfeited if she refuses to discuss the intervention. Document this discussion.
8. Inform the patient about the risks and the recovery time.
9. Refrain from altering records.
10. Personally obtain the consent, not relegating this duty to a nurse or staff member.



Study Questions for Chapter 42

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. It is important for a physician to _____ when counseling a couple who wishes artificial insemination.
 - ☐ A Explain that divorce absolves the husband from child support
 - ☐ B Explain that there is no guarantee of pregnancy if protocol is followed
 - ☐ C Explain that, with screening, birth defects are not possible
 - ☐ D Explain that transmission of STDs is very likely
 - ☐ E Explain that a divorce excludes the husband from access to the child

2. An obstetrician is called at home by a woman who is in labor. Although she has never been to see the obstetrician for a prenatal visit, she would like him to deliver her infant. The obstetrician refuses to attend to her because he is in the middle of dinner. She subsequently delivers a healthy infant at home. If this woman sues the physician for negligence, which of the following would be his best defense?
 - ☐ A Labor is not a disease, so it was not necessary to attend to this pregnant woman
 - ☐ B Because the woman did not come for prenatal visits, she is not entitled to a physician
 - ☐ C Because the woman gave birth to a healthy infant, no harm was done
 - ☐ D The physician never accepted the woman as his patient
 - ☐ E The patient was contributorily negligent in not calling the physician long in advance of active labor

3. A gynecologist has a longstanding relationship with a patient. The woman becomes pregnant but does not inform her gynecologist of her pregnancy and is not scheduled to see him until the next annual visit. One Saturday she calls to report nausea and vomiting but is unable to reach her physician, who is on vacation and has left no other physician to take care of his patients. Three months later the patient goes into preterm labor and delivers a premature infant. The infant ultimately dies 1 month later. In a lawsuit, which of the following statements is the physician's best defense?
 - ☐ A No physician–patient relationship existed
 - ☐ B The physician did not breach any duty owed to the patient
 - ☐ C The premature delivery and fetal death was unrelated to the physician's time on vacation
 - ☐ D A premature infant is not a viable human being
 - ☐ E The woman has not suffered any injuries

4. A 24-year-old, gravida 1, Southeast Asian woman with no known medical problems presents for prenatal care. Her husband is also Southeast Asian. The patient is found to have microcytic anemia. The physician performs a work-up. Iron studies and a hemoglobin electrophoresis return normal and the physician reassures the patient. The pregnancy is uneventful, but shortly after the delivery the infant is found to be jaundiced and symptomatically anemic. The diagnosis of Hb H disease is made. The parents bring a lawsuit. The best way to describe this lawsuit is:
 - ☐ A Wrongful birth
 - ☐ B Wrongful conception
 - ☐ C Wrongful life
 - ☐ D Medical malpractice
 - ☐ E Wrongful counseling



Answers and Explanations

1. **The answer is B** [VI A 2, 4, 5]. The couple who wishes artificial insemination by donor (AID) must be told of the risks of acquiring birth defects due to unknown recessive genes of the donor. There is no guarantee of pregnancy. Even though there is little risk of STD because of screening and quarantined freeze preservation of semen, there is no guarantee against that transmission. It is essential that the husband gives his consent because, in doing so, he is accepting all responsibility for the child born through the donor insemination process. In addition to that responsibility, in case of divorce, the husband maintains his right to visitation and is responsible for child support.
2. **The answer is D** [II B 1 to 4]. For a physician to be sued for negligence, the plaintiff must clear four hurdles. These are (1) that a duty existed; (2) that the duty was breached; (3) that, because of the breach of duty, harm was directly caused; and (4) real damage occurred. In this case, no physician–patient relationship existed because the physician refused to help a person who was not his patient. Although it might be argued that it would have been morally correct for the physician to attend to this woman, the law does not recognize a duty to rescue. A physician–patient relationship must be entered into voluntarily and cannot be coerced on either part.
3. **The answer is C** [II B 1 to 4]. Although the physician was negligent in not having another physician cover for him while he was on vacation, his negligence did not proximately cause his patient’s ultimate injury. Any relationship between the physician’s negligence of not being present and the patient’s premature delivery 3 months later is too remote to establish causation. Because a premature infant was born and lived for 1 month, it is a human being and a legal entity that can maintain a lawsuit. Also, the mother can maintain a lawsuit apart from her infant.
4. **The answer is A** [IV E 6, VII B 2]. The physician may be liable for wrongful birth. Wrongful birth actions are brought by the parents of a child with a congenital defect, alleging that a physician was remiss in genetic counseling, and because of this, a defective child was allowed to be born. In this vignette, the physician failed to appreciate that the patient was in a high-risk group for a hereditary disease; in this case being a carrier for a hemoglobinopathy not detected by hemoglobin electrophoresis. As a result, the condition could not be tested for and the patient did not have the option of termination. In general, these cases have been successful, especially in cases where testing would have been easy such as for alpha-thalassemia. Wrongful life actions that are brought by a child, alleging that no life would have been better than life with congenital defects, have generally been unsuccessful. Compensation prior to these injuries, however, may be granted on negligence theory. In cases involving wrongful conception (namely, parents seeking compensation for a normal child resulting from a failed sterilization), willingness to compensate has been low. In cases in which the resulting child was abnormal, medical expenses for the care of the infant have been granted. Important to the determination of wrongful conception is documentation of whether the mother was informed of the possibility of failure of the sterilization procedure. There is no such term as “wrongful counseling.” Medical malpractice is an umbrella term, and it does not specifically describe this clinical scenario.



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